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Throat Streptococci in Rheumatoid Arthritis

By Auli Toivanen

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publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) are published promptly The papers are published in English, French or German. Acta Medica Scandinavica is published on a non profit basis.

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From the Department of Medical Microbiology and the Department
of Medicine University of Turku Turku, Finland

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CONTENTS

INTRODUCTION

On the etiology of rheumatoid arthritis, a number of diverse concepts and speculations have been presented. During almost seven decades, an infectious agent related to this disease has been sought, but in spite of extensive studies no micro-organism has been accepted as the cause of it (DAWSON 1955 1957 CHRISTIAN 1964) In recent years the question about a latent infection has been put forward. The chronic character of rheumatoid arthritis and the constancy of the rheumatoid factor during the disease suggest that there might be a continued stimulus as an etiologic factor (WILLIAMS & KUNKEL 1962) The relation of the host to the infection might be decisive. Possibly an inherited defect in resistance to a universally distributed agent, for instance some streptococcus, mycoplasma, or virus, might lead to an immunological process resulting in rheumatoid arthritis (THOMAS 1959 FUDENBERG & FRANKLIN 1965, CHRISTIAN *et al* 1968) Such a micro-organism could either belong to the bacteria of the normal human flora or be very similar to them. It has been emphasized that the ability of streptococci to produce systemic disease may be independent of their local aggressiveness without any signs of the infection (JOHNSON 1960) A comparative survey on the throat streptococcal flora and on the relation of the host to this in nonarthritic and rheumatoid arthritis patients thus seems called for No systematic study with detailed identification of the throat streptococci in rheumatoid arthritis has been undertaken. The viridans group streptococci, possibly because of the difficulties in the typing have especially remained outside the scope of the investigation.

The purpose of the present work is to study the possible role of throat streptococci in the etiology of rheumatoid arthritis. This has been made by comparing the throat streptococci in patients with rheumatoid arthritis and in nonarthritic control subjects, and the relation of the hosts to throat streptococcal flora as determined from serum antibodies.

Streptococci and their presence in the human throat

Streptococci are gram positive bacteria, spherical or elliptical in shape, occurring in pairs or in short and long chains. The discoid colonies on solid media show various contours and on blood agar varying hemolysis. Streptococci split different carbohydrates with the production of dextro-rotatory lactic acid carbon dioxide is formed in only very small quantities or not at all. The group of anaerobic streptococci is considered a separate genus, the *Peptostreptococcus* and is not dealt with in this study The genus *Streptococcus* is divided into four main groups the pyogenic, the viridans, the enterococcus, and the lactic group The classification, as far as concerned with the species isolated in the present study is shown in Table 2 (p 14) according to SHERMAN (1937) SWIFT (1952) SEELEMANN (1954) BREED *et al* (1957) and HALLMANN (1961)

The pathogenicity of different streptococci for man varies considerably The most pathogenic species, *S pyogenes* causes a great number of human diseases among others, infections of the upper and lower respiratory tract, septicemia, puerperal fever scarlet fever erysipelas and as sequelae nephritis and rheumatic fever Other pyogenic group streptococci, especially those belonging to the serological Lancefield groups C and G may also have a high pathogenicity but are also often found as commensals or as secondary invaders of traumatized tissues. The viridans group streptococci and enterococci are considered less pathogenic for man than the above mentioned, and the diseases caused by them are often secondary in nature and chronic in duration. They include infections of the upper and lower respiratory tract, endometritis, pyelonephritis, endocarditis and septicemia. The lactic streptococci are common contaminants of milk and are also used in the production of some dairy products. Their human pathogenicity is little if any It is well established that the highly as well as the less pathogenic streptococcal species, can be found in man without any sign of infection. For a more complete view of streptococci, the reader is referred to the works of SWIFT (1952) SEELEMANN (1954) BREED *et al* (1957) and HALLMANN (1961)

The microbial flora on the mucosa of the human throat is both concentrated and varied (BERGER 1955 BREED *et al.* 1957 BURNETT & SCHERP 1968) Generally present are species of the genera *Streptococcus, Staphylococcus Diplococcus, Corynebacterium Actinomyces Neisseria Veillonella, Haemophilus* M*coplasma* and various yeasts. Colif bacteria and even some protozoa may

be found transitionally. Of special interest is the fact that many pathogenic bacteria can be found in the throat of completely healthy carriers; such as for instance *Streptococcus pyogenes*, *Staphylococcus aureus*, *Neisseria meningitidis* and *Corynebacterium diphtheriae*. Among the normal human throat flora by far the most abundant are the streptococci, and from these the viridans group streptococci (SWIFT 1952, BERGER 1955, KORTEKANGAS 1959, BURNETT & SCHERP 1968).

Isolation of streptococci in rheumatoid arthritis

Infection was one of the first theories on the etiology of rheumatoid arthritis. The joints involved and the blood were self-evident objects for investigation and innumerable blood and synovial fluid cultures have been carried out by various methods. Earlier interest was shown mainly in bacteria but in recent years besides them, it has also been focused on viruses and *mycoplasmae*. The great risk of contamination and the possibility that the isolated microorganisms are in fact secondary invaders to the joints made less constant by rheumatoid arthritis make the results of these studies questionable (Editorial Lancet 1967).

The earliest efforts to isolate microorganisms from rheumatoid arthritis patients are reviewed by CECIL *et al.* (1929): the majority of them were cultural studies of the blood and synovial fluid. The results were, however contradictory. In 1929 CECIL *et al.* isolated a "typical strain" of streptococcus from blood of more than 60 per cent of patients with rheumatoid arthritis. They were also able to culture this streptococcus from the joints and local foci of some patients. In rabbits this strain caused a nonsuppurative polyarthritis. Rheumatoid sera agglutinated the "typical strain" in high titres (CECIL *et al.* 1931). These results could not, however be repeated later (DAWSON *et al.* 1932a, FRASER 1943) and after extensive new experiments CECIL retracted the earlier results and considered a contamination as a cause of them (ANGEVINE *et al.* 1942).

From the throat of rheumatoid arthritis patients different streptococci have been isolated. Most attention has been paid to the strains of the pyogenic group and enterococci. OLHAGEN (1947) isolated some occasional strains of *S. faecalis* from the throat of rheumatoid arthritis patients. DAVIDSON *et al.* (1949) studied the throat bacterial flora of 100 rheumatoid arthritis patients and 100 control patients. The predominant flora consisted of hemolytic, greening and nonhemolytic streptococci without any difference between the two groups. They identified the strains isolated only on the basis of hemolysis. BEEUWKES *et al.* (1959) cultured the throat streptococci from 30 rheumatoid arthritis patients and 30 healthy control patients, but studied only serum antibodies to these without identifying the bacteria. CABAU (1959) compared the throat streptococci of 258 patients with different rheumatic disorders to the streptococci of 214 healthy persons. The great majority of the isolated strains were viridans strep-

streptococci in the patient group the incidence of strains belonging to the Lancefield groups A, C and G was greater than in the control patients, but the difference was not significant. The author gives neither the number of the patients with rheumatoid arthritis nor the criteria used in the identification of the isolated strains. JONSSON (1960) studied throat hemolytic streptococci in patients with arthritis of unknown etiology. He isolated 43 hemolytic strains, of which 39 could be classified serologically according to the Lancefield system; of these eleven were isolated from patients with rheumatoid arthritis. These belonged to the Lancefield groups A, B, C and G. In a follow-up study FRANÇOIS (1965) found group A, C and G streptococci in the throat of 23 out of 54 rheumatoid arthritis patients. This was significantly more than the number of corresponding isolations in the control patients, but in the prevalence of pyogenic group streptococci no difference was found between the groups. He studied only the β-hemolytic streptococci and presents no data about the prevalence of other strains.

SVARTZ (1938, 1960) isolated from the throat, feces and joints of patients with rheumatoid arthritis a polymorphous diplococcus and considered it *S. agalactiae*; three of fifteen strains gave a positive precipitation reaction with group B antiserum. VENTERS & GOOD (1963) made an attempt to confirm the findings of SVARTZ. In their extensive studies from throat, blood and synovia they could not isolate *S. agalactiae* or any other micro-organism which could be considered a cause of rheumatoid arthritis. HOUBA *et al.* (1964) did not find any hemolytic throat streptococci in 107 patients with rheumatoid arthritis and 33 control subjects.

Focal infection in the upper respiratory tract if often caused by streptococci. That focal infection has a role in the cause of rheumatoid arthritis has been another theory gaining much support. In 1938, CECIL & ANGEVINE studied the incidence of infective foci in 200 rheumatoid arthritis patients and found a definite focus only in 90 per cent and a questionable focus in 10 per cent of the cases. A study by DAVIDSON *et al.* (1949) on the focal infection in rheumatoid arthritis included 100 rheumatoid arthritis patients and 100 control patients. The prevalence of foci in the upper respiratory tract was 44 per cent in the rheumatoid and 43 per cent in the control group. An extensive investigation of the Scientific Advisory Committee of the Empire Rheumatism Council (1950) resulted in the same finding: no clear correlation of focal infection to the prevalence of rheumatoid arthritis could be observed. The focal infection seems to play a comparatively unimportant role in rheumatoid arthritis. The infection might however trigger an abnormal autoimmune mechanism resulting in arthritis (Editorial, Lancet 1967).

Streptococcal antibodies in rheumatoid arthritis

Since the first reports on isolation of streptococci from patients with rheumatoid arthritis, antibodies against

these bacteria and especially against the pyogenic group streptococci have been extensively studied. No significant increase of antistreptolysin-O (McEwen *et al* 1935, Harris *et al* 1950 François 1965, Stevens 1965) antihyaluronidase (Harris *et al* 1950, Faber 1953) or antifibrinolysin (Myers *et al.* 1935, McEwen *et al* 1936, Perry 1940 Houba *et al.* 1964) has been found in rheumatoid sera. The failure to find any difference between rheumatoid arthritis patients and control patients in the titres of antibodies to the toxins of the pyogenic group streptococci indicate that these bacteria have hardly any role in this disease (Wallis 1946a)

Precipitins against extracts from pyogenic group streptococci have been detected in rheumatoid sera but they have been considered nonspecific as the same serum may precipitate extracts of more than one serological group (*Chasis* & McEwen 1936, Bruce & Caswell 1940, *Wallis 1947a) Chasis & McEwen* (1936) and *Wallis (1946b)* demonstrated that the serum of patients with rheumatoid arthritis may precipitate itself even in saline. Wallis (1947a) considered it probable that rheumatoid sera contain a factor that enhances the action of normally present antibodies. Surely we deal here with the same factor that promotes the agglutination reaction, the rheumatoid factor Bezuwken *et al* (1957) demonstrated by passive hemagglutination, using an acetamide extract from a Lancefield group A strain a significantly higher percentage of positive reactions with rheumatoid than control sera. Also with complement fixation reaction, the rheumatoid sera revealed antibodies to the extract more often than the control sera. The antigen used was not group-specific and also gave positive precipitation reactions with antisera against extracts from group C and D streptococci. The extracts prepared from gram-negative rods and pneumococci did not react with rheumatoid sera whereas pyogenic group streptococci, viridans group streptococci and staphylococci often gave an extract reacting positively (Bezuwken *et al* 1959) The authors also isolated throat streptococci from 20 rheumatoid arthritis patients and 30 control patients, and prepared an extract of a mixed culture from each patient's streptococci. With passive hemagglutination, three rheumatoid sera, but none of the control sera, gave a positive reaction with the extract from the patient's own streptococci. The authors considered that it was possible certain persons may produce antibodies against their own streptococcal throat flora, and that these antibodies play a part in the pathogenesis of rheumatoid arthritis.

Cecil *et al* (1931) observed that rheumatoid sera strongly agglutinated their "typical streptococci Many other authors thereafter described the ability of rheumatoid sera to agglutinate pyogenic group streptococci isolated from rheumatoid arthritis or other patients (Dawson *et al* 1932b, *Ziff* 1957) Enterococci (Olhagen 1947) staphylococci (Oker Blom 1948) nonencapsulated pneumococci (Dawson *et al.* 1932b, Wallis 1946c) and even collodion particles (Wallis 1946b) are also agglutinated Wallis (1947b) consid-

Patients

The 70 patients with rheumatoid arthritis included in the study are divided into the rheumatoid groups I and II according t the duration of the disease They ha the respective control groups I and II. Characteristics of these groups are presented in T ble 1.

The rheumatoid group I consists of patients treated at the Department of Medicine Uni-

TABLE 1. Number of patients in the different groups and some characteristics of them.

	Rheumatoid group I	Control group I	Rheumatoid group II	Control group II
Number f patients	35	35	32	32
Male	14	14	11	14
Female	4	4	21	19
Mean age ± S.D. (years)	43.[illegible]±16.3	49.4±15.[illegible]	49.4±9.[illegible]	46.9±12.4
Duration of rheumatoid arthritis				
< 1 year	19	—	—	—
1—5 years	19	—	—	—
> 5 years	—	—	32	—
Classification f rheumatoid arthritis				
Probable	5	—	1	—
Definit	13	—	9	—
Classical	20	—	22	—
Latex reaction				
—	8	34	—	29
+	5	3	—	—
++	3	1	—	1
+++	15	—	13	
++++	7	—	19	—
Waaler Rose titre				
< 32	1	29*	—	30
32 — 64	8	7	1	1
128 — 256	9	1	[illegible]	1
512 — 1024	3	—		—
2048 — 4096	1	—	15	—
> 4096	—	—	9	—

One serum was [illegible]ted

versity of Turku, with symptoms of rheumatoid arthritis for less than five years. The samples were collected during the period from July 1964 to September 1967. An attempt was made to find cases with as short a duration of the disease as possible. Due t this, a great number of the cases in this group were probable when classified according to the criteria of the American Rheumatism Association (ARA) (Ropes et al. 1959).

The rheumatoid group II included patients with the duration of the disease of more than five years and with definitely positive latex and Waaler Rose reactions. Samples from these patients were collected in May 1965 at the Rheumatism Foundation Hospital, Heinola, except for samples from two patients treated t the Department f Medicine University of Turku.

Subjects corresponding with the rheumatoid group patients in age and sex were selected for the control groups. It was not always possible t have an exactly corresponding control subject t each patient (Table 1) since samples in the control groups were collected simultaneously with those of the respective rheumatoid groups. The diagnoses f the control patients can be grouped as follows cardiovascular disease (29 patients) cerebrovascular disease (5) gastrointestinal disorder (8) malignancy (6) vertigo (3) liver disease (3) toxic goiter (2) obesity (2) nd diabetes mellitus (1). In the group f liver diseases one suffered from cirrhosis, one had hepatic reaction due to chlorpromazin and one had gall stones. Only the first one was icteric and had positiv (++) latex test; the Waaler Rose reaction was negativ. Eight patients ere in the hospital for examination only and had no detectable disease. N subject with joint symptoms are included in the control groups. All were treated t the Department of Medicine, University f Turku.

Patients with symptoms of respiratory tract infection or on antibiotic or cytostatic therapy are not included.

Throat swabs and blood samples

The throat swab specimens were taken in the morning before the patient had rinsed her mouth or eaten anything. The tonsils and the throat were swabbed, and the sample was immediately cultured on blood and chocolate agar plates.

At the same time as the throat swab specimens blood samples were taken by vein puncture. They were allowed to clot, the serum was removed and stored at —20 C.

Bacteriological methods

The 5 per cent sheep cell blood agar and chocolate agar (heated blood agar) plates used were prepared according to HALLMANN (1953). All cultures were incubated at 37°C except the tubes for the growth at 45 C. The chocolate gar plates were incubated in an atmosphere f carbon dioxide. Strains growing as typical streptococcal colonies on blood and chocolate agar insensitive to optochin, and forming chains f gram-positive cocci in broth, were tested further. Subcultures were made from all susceptible colonies macroscopically different on the primary plates. All strains originally isolated from chocolate agar plates grew also on blood agar and in normal atmosphere. In the rheumatoid group I and in the control group I all strains isolated from both chocolate and blood agar were tested separately. In the rheumatoid group II and in the control group II all strains from each patient were cultured on one blood agar plate to compare them with each other and those with an identical hemolysis and macroscopically similar colonies were considered as the same strain. This could be done on the basis f the experience gained with the streptococci from rheumatoid and control group I which had been analysed first the majority of the strains isolated from chocolate agar plates in these groups proved to be identical with the strains isolated from blood agar plates.

All strains ere freeze-dried. For typing or for preparing antigen the strains ere taken from ampoules unless fresh culture was at hand.

In the identification of the streptococci, the media and procedures listed below were employed (Table 2).

MATERIAL AND METHODS

Patients

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Classical	20	—	22	—
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—	8	34	—	29
+	5	3	—	—
+ +	3	1	—	1
+ + +	13	—	13	
+ + + +	7	—	19	—
Waaler-Rose titre				
< 32	17	29*	—	30
3 — 64	8	7	1	1
128 — 256	9	1	2	1
51 — 1024	3	—	2	—
2048 — 4096	1	—	18	—
> 4096	—	—	9	—

One serum as not tested.

Colony form and hemolysis on 5 per cent sheep cell blood agar. Incubation time was two days.

Growth at 45°C was tested using trypsine broth according to HALLMANN (1953). The tubes were incubated at 45 C for three days. Visible growth was recorded as positive reaction. This test was preferred for the ability to survive 60°C for 30 minutes for reasons given by BRADHAUER (1950) and HIRSCHER *et al.* (1967).

Growth in 0.1 per cent methylene blue milk. The medium was prepared according to HALLMANN (1953) and the tubes were incubated at 37°C for three days. The reaction was considered positive already after a partial reduction of the dye.

Growth in broth with 4 per cent or 6.5 per cent NaCl (BRADHAUER 1950). Incubation time was three days. Visible growth was recorded as positive reaction.

Growth on blood agar with 10 per cent or 40 per cent bile (SEELEMANN 1954). The plates were incubated for two days.

Alkali tolerance (BRADHAUER 1950). Usual broth adjusted to pH 9.6 with sodium hydroxide was used. Incubation time was three days and visible growth was recorded as positive reaction.

Reaction in litmus milk (CRUICKSHANK 1960). Incubation time was three days; acid formation, reduction and clotting were observed.

Liquefaction of gelatin (HALLMANN 1953). After making stab-cultures, the media were incubated at 37°C for three days to obtain good growth. The tubes were then cooled at 4 C for two hours and examined for liquefaction.

Splitting of sodium hippurate. The sodium hippurate medium was prepared according to HALLMANN (1953) and benzoate was detected according to COWAN & STEEL (1965). The incubation time was three days.

Production of ammonia from peptone was tested according to SEELEMANN (1954).

Fermentation of the following substances: glucose, maltose, lactose, sucrose, salicin, esculin, trehalose, inulin, raffinose, arabinose, glycerol, mannitol, sorbitol and starch. The media with brom thymol blue as the indicator were prepared according to CRUICKSHANK (1960). The incubation time was three days.

Growth on 5 per cent sucrose agar (GARROD 1950). Tryptose agar with 5 per cent sucrose was used. The plates were incubated at 37°C for two days and then in room temperature for one week. Readings to detect large mucoid colonies were made every day. This reaction was considered decisive for the identification of *S. salivarius*.

Optochin test. To exclude the pneumococci, the optochin sensitivity of all isolated strains was tested by the disc method (LUND 1959). Each disc with a diameter of 5 mm contained 5 µg optochin. Strains giving inhibition zones ≥ 15 mm were considered as pneumococci and discharged.

Serological grouping of the streptococci. To determine the Lancefield group precipitation reactions were carried out by double diffusion (KRAUSE & RAUNIO 1967) using 1 per cent Special Agar-Noble (Difco) in phosphate buffer pH 7.4, M 0.15. Streptococcal antigens were prepared by autoclaving (RANTZ & RANDALL 1955). Commercial antisera (Wellcome) for the groups A, B, C, D, E, F, G, H, K, L, M, N, O, P and Q were used. The precipitates were allowed to develop in a moist chamber for two days. Positive controls with the extracts from the type strains (National Collection of Type Cultures, London) were included in each test. Each strain was tested against the antisera possible to give positive reaction on the basis of the biochemical tests. If a strain was serologically typable to a Lancefield group, this was considered conclusive, if the other characteristics of the strain were not in obvious conflict. In fact, this was only once the case: a strain was serologically type Q but its physiological pattern was that of *S. salivarius*, and the strain is recorded as *S. salivarius*. The great majority of the streptococci studied were not typable to the Lancefield groups, and their differentiation had to be based on the physiological patterns.

The criteria used for the identification of the streptococci. The identification of streptococci into the pyogenic, viridans, enterococcus and lactic group, and the further division of these into the different species is based

on the views of SHERMAN (1937) SWIFT (1952) SEELEMANN (1954) BREED et al. (1957) and HALLMANN (1961). For identification of each isolated strain, that is, for placing it into some species, its physiological properties were compared with those described by the aforementioned authors. Table _ shows the classification of streptococci, the characteristics studied and the criteria used in the identification of each strain; species not found in this study are excluded. It must be stressed that no single reaction alone can be decisive although each species usually has some relatively constant reactions typical of it, and these can be considered decisive when all the other features are not in obvious conflict.

The pyogenic group streptococci were differentiated from the other groups by their biochemical characteristics, the usual β-hemolysis on blood agar and by positive precipitation reactions revealing the Lancefield group. Thus *S. pyogenes* was easily identified. For *S. galactiae* the group B and the ability to split sodium hippurate as well as growth on 40 per cent bile blood agar were decisive. From the group C streptococci, decisive for *S. dysgalactiae* was α-hemolysis and for *S. equisimilis* the combination of β-hemolysis and fermentation of trehalose. The two strains belonging to the Lancefield group G were considered the "large colony" type because of the typical colonies and fermentation of starch but not raffinose. *S. anginis* shows variability in its reactions (SHERMAN 1937, SWIFT 1952) and thus the most important criterion for it was the serological type H. The biochemical variability of group Q streptococci appears from the descriptions by SEELEMANN (1954) and GUTHOF (1955); the serological grouping was considered the main criterion for them.

The most important feature of viridans group streptococci was considered the lack of any positive typical characteristics, and especially the negative precipitation reactions with all antisera used. *Streptococcus* MG was identified on the basis of biochemical tests according to MIRICK et al. (1944). Characteristically *S.* MG grows on bile blood agar but not in broth with pH 9.6 or containing NaCl 4 per cent, or at 45°C and does not ferment inulin or raffinose. For *S. salivarius* the main criteria were the usual nonhemolysis, growth on 10 per cent and often on 40 per cent bile blood agar, prompt acidification and curdling of litmus milk, fermentation of glucose, maltose, sucrose, raffinose and inulin, and growth as large mucoid colonies on 5 per cent sucrose agar. From *S. salivarius* the resembling *S. bovis* was differentiated by its ability to grow at 45°C and on 40 per cent bile blood agar and by the inability to ferment inulin. The identification of a strain as *S. mitis* had to be based on excluding the other possibilities, according to GUTHOF (1960). The most important criteria that excluded the *S. salivarius* were strong greening on blood agar, faint or no growth on 10 per cent and no growth on 40 per cent bile blood agar and the inability to ferment inulin. Among the mitis-streptococci, I have separated a rather homogenous group and called it an inactive variant of *S. mitis*. It comprises of 46 strains that were characterized by growth as small, nonhemolytic colonies or very weak α-hemolysis, and from which 33 gave negative reactions in all fermentation tests, eleven were negative in all fermentation tests except in one and two strains fermented two substances. That the inactivity was not due simply to poor growth was confirmed by repeated test series and cultures from the test media.

The identification of enterococci was based upon their growth characteristics and the serological type D. *S. faecalis* was recognized by its α- or nonhemolysis, splitting of esculin and inability to liquefy gelatin.

Tests for rheumatoid factor

The Waaler-Rose test was performed according to ARO (1961). Amboceptor from one rabbit was used. For sensitization of the sheep red cells, a dilution of the amboceptor corresponding 1/3 of the minimum agglutinating dose was used. The sera studied were diluted by the serial twofold transfer method changing to a new pipette after each third tube. Standard serum with a known titre was included in each series. The titres are expressed as reciprocals.

For *the latex test*, the one-tube method with

the patient's own gammaglobulin was employed (BROMAN & PLOTZ 1958). Acrylplast particles of Bofors, Nobelkrut, Sweden, were used. A positive and negative control was included in each test series.

Tests for streptococcal antibodies

Precipitation reaction

Precipitation reaction was used since the anti-gammaglobulin nature of rheumatoid factor has little possibility of manifesting itself in this.

Precipitins against the patient's own streptococci were studied by double diffusion in agar as described above for the serological grouping of streptococci. The serum of each patient was tested undiluted and in a 1:4 dilution, against the autoclave extract of each strain.

Indirect immunofluorescence tests

Indirect immunofluorescence technique was used because identification of the immunoglobulin class of the reacting antibody can readily be made with the aid of this test.

The procedure described by GINSBURG et al. (1960) for indirect immunofluorescence was used with minor modifications. The strain used as antigen was grown overnight on blood agar. From a saline suspension incubated for 30 minutes at 37°C, three smears were made on an UV glass slide. The smears were air-dried and fixed by gentle warming in a flame. One of the smears was covered with a dilution 1:10 of the serum to be tested, the second one with a dilution 1:100, and the third one served as the negative control for the nonspecific fluorescence. The slide was incubated for 15 minutes in a moist chamber and washed for three ten-minute periods in phosphate buffer pH 7.2, M 0.15. Next, all three smears were covered with the fluorescein-isothiocyanate-conjugated (FITC) antiserum, and incubated for 15 minutes in a moist chamber. Finally the slide was rinsed three times as above with the phosphate buffer and air-dried.

Immediately after the preparation, the smears were examined under a Zeiss fluorescence microscope (HBO 200 light source with BG 38/2.5 and BG 3/4 primary filters and a Zeiss 50 secondary filter; magnification 63 × 8). The fluorescence intensity was scored as follows: 3 — bright yellow-green fluorescence; 2 — visible fluorescence; 1 — barely visible fluorescence; 0 — no fluorescence. A reaction was considered positive when the difference between the scores given by it and the negative control was at least two. Nonspecific fluorescence was recorded positive with a score of 2 or 3.

The serum of each patient, in dilutions 1:10 and 1:100, was tested separately against all different streptococcal strains isolated from the patient's throat.

FITC-anti-human-immunoglobulin was supplied by Associate Professor J. A. GRÖNROOS. This antiserum reacted with IgG, IgM, IgA and some other serum proteins when tested with immunoelectrophoresis. FITC-anti-human IgG and FITC-anti-human IgM were commercial products of Behringwerke. These antisera were monospecific in immunoelectrophoresis but the latter gave a very faint reaction with IgG when tested against purified IgG, IgM and IgA by double diffusion in agar. All three were rabbit sera.

Positive controls were included in each day's tests: for FITC-anti-immunoglobulin and FITC-anti-IgM *Salmonella paratyphi B* and for FITC-anti-IgG *Streptococcus salivarius*, both with a homologous human antiserum 1:10 and 1:100.

Statistics

For the statistical analysis, the Student's t-test was employed.

Streptococci isolated

The characteristics given in Table 2 were studied from 564 streptococcal isolates, 399 in the groups I and 165 in the groups II. They proved to be 242 different strains, 129 in the groups I and 113 in the groups II (Table 3). From the strains isolated, 114 were from the rheumatoid and 128 from the control groups. Their distribution in the patient groups and different species is presented in Table 3.

The majority, 209 strains, belongs to the viridans group; the most often represented species are *S. salivarius*, *S. mitis* and that named an inactive variant of *S. mitis*. There is no difference in the frequency of different streptococci between the rheumatoid and control groups. Neither can any difference be found when the rheumatoid groups I and II are compared with the respective control groups, nor between the patients having had the disease for less than one year and those with the disease of longer duration. The rheumatoid groups I and II cannot be directly compared with each other since the samples were not collected at the same time.

Twenty-one strains of the pyogenic group and two enterococcal strains were isolated. Their presence is too scanty for conclusions to be drawn from the distribution in the different groups. Only two strains of *S. pyogenes* were isolated. The number of the *S. agalactiae* is on the other hand higher: ten strains, from which seven are in the control groups and three in the rheumatoid groups.

Ten strains could not be grouped to any species. From these three were isolated in the rheumatoid and seven in the control groups.

Table 4 shows characteristics of the three most common species, *S. salivarius*, *S. mitis* and the inactive variant of *S. mitis*, according to their origin. The individual combinations of the reactions for each separate strain are not shown in the table, but they did not reveal any special variant characteristic for the rheumatoid patients.

Streptococcal antibodies

Precipitation reaction

Precipitins against the antigens prepared from the patient's own streptococci were found in five rheumatoid and seven control sera (Table 5). The tests were carried out using a separate extract of each strain. There is no significant difference between the rheumatoid and control groups. Table 6 shows that the distribution of positive reactions into different species corresponds roughly to the number of strains isolated in each species.

TABLE 1. Number of different streptococci isolated in the different groups.

Species	Rheumatoid group I Duration of disease < 1 year	Rheumatoid group I Duration of disease 1—3 years	Rheumatoid group I Total	Control group I	Rheumatoid group II	Control group II	Rheumatoid groups I+II	Control groups I+II	Total
S. pyogenes	1	—	1	1	—	—	1	1	2
S. agalactiae	1	2	3	7	—	—	3	7	10
S. dysgalactiae	1	—	1	—	—	—	1	—	1
S. equisimilis	—	—	—	1	—	—	—	1	1
S. "large colony" group G	1	—	1	—	1	—	2	—	2
S. sanguis	—	—	—	1	1	—	1	1	2
S. haemolyticus, group Q	—	—	—	1	2	—	2	1	3
S. MG	1	1	2	—	2	—	4	—	4
S. salivarius	3	5	8	11	7	5	15	16	31
S. mitis	20	15	35	36	23	29	58	65	123
S. mitis, inactive variant	1	4	5	7	10	18	21	25	46
S. bovis	2	—	2	1	1	1	3	2	5
S. faecalis	—	—	—	2	—	—	—	2	2
Unidentified	1	—	1	3	2	4	3	7	10
Total number of strains	31	28	59	70	55	68	114	128	242
Number of patients	*19*	*19*	*38*	*38*	*32*	*32*	*70*	*70*	*140*

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	1	6		5	9	6
[illegible]	4	4	15	2	3	3
[illegible]		4	1	11	3	3
[illegible]		3	1	9	1	5
[illegible]	2		4		1	—
[illegible]	15	15	—	4	3	4
[illegible]		6	1	13		3
[illegible]	3		10	17	5	1
[illegible]	15	14	2 wr	4 wr	3 wr	4 wr
[illegible]			—	—	—	—
[illegible]	2	—	5	3	2	—
[illegible]	1	7	4	10	—	4
[illegible]	15	14	1	54		4
[illegible]	14	15	13		—	2
[illegible]	11	14	4	5	1	—
[illegible]	15	14	14	9	1	1
Hallet	12	11	11	14	—	—
[illegible]	10	12	4	10	—	1
[illegible]	9	1	14	1	—	—
[illegible]			3	13	—	—
[illegible]	13	14	17	21	—	—
[illegible]	3	4	11	1	—	—
[illegible]	—	—		7	—	—
[illegible]	—	1	—	4	—	—
[illegible]		—			—	—
[illegible]						—

TABLE 5. Occurrence of streptococcal precipitins in the different groups, when the patient's serum 1 4 was tested gainst the extracts f his ow strains. The extract of each strain was tested separately. All differences between the rheumatoid groups and the respecti controls are statistically insignificant ($P > 0.05$)

	Rheumatoid group I	Co trol group I	Rheumatoid group II	Control group II	Rheumatoid groups I+II	Control groups I+II
Number of the strains, against which precipi tins were found, per number of strains tested.	3 /39	5 /70	/55	5/35	5 /114	10 /125
Number f sera with precipitins against at least one strain, per number of sera tested.	3*/35	2/35	2 /32	5/35	5 /70	7/70

Includes one reaction achieved with the undiluted serum only
Includes two reactions achieved with the undiluted serum only

TABLE 6. Species distribution f streptococcal precipitins.

Species	Rheumatoid groups I+II	Control groups I+II
S. pyogenes	—	—
S agalactiae	—	1
S dysgalactiae	—	—
S equisimilis	—	—
S. "large colony" group G	—	—
S. sanguis	—	—
S. haemolyticus, group Q	—	—
S. MG	1	—
S. salivarius	1	2
S m tis	3	4
S. mitis, inactive variant	—	2
S. bovis	—	1
S faecalis	—	—
Unidentified	—	—
Total	5	10

Immunofluorescence tests with anti-immunoglobulin

Initially serum antibodies against each patient's own streptococci were studied in the rheumatoid group I and in the control group I using FITC-anti immunoglobulin. The results (Tables 7 and 8) do not reveal any difference between the groups.

Immunofluorescence tests with anti IgG and anti IgM

From the early results of this work, it seemed to me that rheumatoid sera could give positive reaction with the fluorescence anti-immunoglobulin technique more often than control sera. For this reason, and to establish the immunoglobulin class of the antibodies detected,

TABLE 7 Occurrence of antibodies t the patient own streptococci, studied ith indirect fluorescence technique usi g FITC-anti-immunoglobulin. The results are expressed the umber f trains against which antibodies ere found, per number f strains tested.

Fluorescence	Rheumatoid group I	Control group I	P
Positive serum 1 10	38/56 (68 %)	34/63 (54 %)	> 0.05
Positi serum 1 100	[illegible]/56 (1[illegible] %)	9/63 (14 %)	> 0.05
Nonspecific	3/[illegible]9	7/[illegible]0	

Includes those positi with serum 1 100

TABLE 8 Occurrence f antibodies t the patie t ow streptococci, studied with indirect fluorescence technique using FITC ti immunoglol lin. The results are pressed as the umber of sera giving positiv reaction ith at least one strain, per umber f sera tested.

Fluorescence	Rheumat id group I	Control group I	P
Positi serum 1 10	30/39 (79 %)	[illegible]/39 (71 %)	> 0.05
Positive serum 1 100	7/39 (18 %)	8/39 (1 %)	> 0.05

Includes those positiv with serum 1 100.

TABLE 9 Occurrence of antibodies t the patient' own streptococci, studied with indirect fluorescence technique using FITC-anti IgG. The results are expressed as the umber of strains against which antibodies were found, per umber of strains tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Control II	P	Rheumatoid groups I+II	Control groups I+II	P
Positive, serum 1 10	23/53 (43 %)	25/63 (40 %)	> 0.05	17/54 (31 %)	20/56 (36 %)	> 0.05	40/107 (37 %)	45/117 (38 %)	> 0.05
Positive, serum 1 100	11/53 (21 %)	13/63 (21 %)	> 0.05	3/54 (6 %)	4/56 (7 %)	> 0.05	14/107 (13 %)	17/117 (15 %)	> 0.05
Nonspecific	6/59	8/70		1/55	3/58		7/114	11/128	

Includes those positiv with serum 1 100.

TABLE 10 Occurrence f antibodies t the patient's own streptococci, studied ith indirect fluorescence technique using FITC-anti IgG. The result are expressed as the number f sera giving a positive reaction with t least one strain, per umber f sera tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Control group II	P	Rheumatoid groups I+II	Control groups I+II	P
Positiv serum 1 10	22/38 (58 %)	19/38 (50 %)	> 0.05	13/32 (41 %)	17/32 (53 %)	> 0.05	35/70 (50 %)	36/70 (51 %)	> 0.05
Positive, serum 1 100	11/38 (29 %)	11/38 (29 %)	> 0.05	2/32 (6 %)	4/32 (13 %)	> 0.05	12/70 (10 %)	15/70 (21 %)	> 0.05

Includes those positive lth serum 1 100

Immunofluorescence tests with anti-immunoglobulin

Initially serum antibodies against each patient's own streptococci were studied in the rheumatoid group I and in the control group I using FITC-anti immunoglobulin. The results (Tables 7 and 8) do not reveal any difference between the groups.

Immunofluorescence tests with anti IgG and anti IgM

From the early results of this work, it seemed to me that rheumatoid sera could give positive reaction with the fluorescence anti immunoglobulin technique more often than control sera. For this reason, and to establish the immunoglobulin class of the antibodies detected,

TABLE 7 Occurrence of antibodies to the patient's own streptococci, studied with indirect fluorescence technique using FITC-anti immunoglobulin. The results are expressed as the number of strains against which antibodies were found, per number of strains tested.

Fluorescence	Rheumatoid group I	Control group I	P
Positive serum 1:10	[illegible]9/56 (65 %)	34/63 (54 %)	> 0.05
Positive serum 1:100	7/56 (1[illegible] %)	9/63 (14 %)	> 0.05
Nonspecific	3/ 9	7/70	

Includes those positive with serum 1:100

TABLE 8 Occurrence of antibodies to the patient's own streptococci, studied with indirect fluorescence technique using FITC-anti immunoglobulin. The results are expressed as the number of sera giving positive reaction with at least one strain, per number of sera tested.

Fluorescence	Rheumatoid group I	Control group I	P
Positive serum 1:10	30/38 (79 %)	[illegible]7/38 (71 %)	> 0.05
Positive serum 1:100	7/38 (19 %)	8/38 ([illegible]1 %)	> 0.05

Includes those positive with serum 1:100.

TABLE 11. Occurrence of antibodies to the patient's own streptococci, studied with indirect fluorescence technique using FITC-anti-IgM. The results are expressed as the number of strains against hich antibodies were found, per umber f strains tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Control group II	P	Rheumatoid groups I+II	Control groups I+II	P
Positiv serum 1 10	13/50 (26 %)	7/59 (13 %)	> 0.05	14/53 (27 %)	3/56 (5 %)	0.003	27/103 (26 %)	10/115 (9 %)	0.001
Positive, serum 1 100	5/50 (10 %)	4/59 (7 %)	> 0.05	3/53 (6 %)	2/56 (4 %)	> 0.05	8/103 (8 %)	6/115 (5 %)	> 0.05
Nonspecific	9/58	11/70		3/56	2/53		12/114	13/125	

Includes those positiv ith serum 1 100.

TABLE 12. Occurrence f antibodies to the patient's own streptococci, studied with indirect fluorescence technique using FITC anti-IgM. The results are expressed as the umber f sera giving positive reaction with t least one strain, per number of sera tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Co trol group II	P	Rheumatoid groups I+II	Control groups I+II	P
Positi e, serum 1 10	12/38 (32 %)	6/38 (16 %)	> 0.05	11/32 (34 %)	3/32 (9 %)	0.01	23/70 (33 %)	9/70 (13 %)	0.003
Positive, serum 1 100	4/38 (11 %)	3/38 (8 %)	> 0.05	3/32 (9 %)	2/32 (6 %)	> 0.05	7/70 (10 %)	5/70 (7 %)	> 0.05

Includes those positive with serum 1 100.

the indirect immunofluorescence tests were extended to the use of FITC-anti-IgG and FITC-anti IgM. In the groups II FITC-anti-immunoglobulin was used no more. The results (Tables 9 to 12) are expressed as the number of positive reactions calculated per streptococci and per sera.

Antibodies of IgG class were found against 31 to 43 per cent of all streptococcal strains when the patient's serum was used in a dilution 1:10 (Table 9). With a 1:100 dilution the corresponding percentages ranged from 6 to 21. Results in Table 10 reveal that 41 to 68 per cent of the persons tested had IgG antibodies against at least one strain occurring in their throat. There is no difference between the respective rheumatoid and control groups in the occurrence of streptococcal IgG antibodies.

The prevalence of IgM class antibodies to the throat streptococci is not as common as that of IgG: only 13 per cent of the control persons had detectable IgM antibodies against at least one strain of their throat. Positive reactions with sera 1:10 were significantly more often observed in the combined rheumatoid groups than in their controls, both when the results are counted per streptococci ($P \approx 0.001$, Table 11) and per sera ($P \approx 0.005$, Table 12) studied. This is due especially to the differences between the rheumatoid group II and their controls. The same tendency is to be seen in the rheumatoid group I but the difference to the control group is not statistically significant.

Th[illegible] distribution of the strains reveal[illegible] immunofluorescence reactions is quite even, roughly corresponding to the total number of strains in each species (Tables 13 and 14). One exception can be mentioned: IgG antibodies to *S. agalactiae* were found perhaps relatively more often than to other species, in nine out of ten cases. The distribution of antibodies is similar in the rheumatoid and control groups. Likewise no difference was found between the groups I and II, therefore only the combined figures are presented.

Association to the rheumatoid factor of the antibodies detected by immunofluorescence

Rheumatoid factor is a complex of different proteins, the vast majority of which belong to the IgM class globulins and the rest to IgG and IgA (KUNKEL & TAN 1964, HEIMER & LEVIN 1966). Antibodies of IgM class against the throat streptococci were more often detected in rheumatoid arthritis than in the control patients. This naturally raises a question about the correlation of these antibodies and the rheumatoid factor. Therefore the number of positive reactions with FITC-anti-IgG and FITC-anti IgM have been compared with the level of rheumatoid factor in the corresponding sera.

No correlation between the positive reactions obtained with FITC-anti-IgG and the titre of the latex reaction can be seen (Table 15). On the contrary the number of positive reactions with FITC-anti IgM is greater for the sera giving a clearly positive latex reaction than for those with a negative or weak latex

TABLE 11. Occurrence f antibodies t the patient's own streptococci, studied with indirect fluorescence technique using FITC-anti-IgM. The results are expressed as the umber f strains gainst which antibodies are f und, per umber f strains tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Control group II	P	Rheumatoid groups I+II	Control groups I+II	P
Positi e, serum 1 10	13/50 (26 %)	7/58 (12 %)	> 0.05	14/53 (27 %)	3/56 (5 %)	0.003	*7/103 (26 %)	10/115 (9 %)	0.001
Positive serum 1 100	5/50 (10 %)	4/59 (7 %)	> 0.05	3/53 (6 %)	2/56 (4 %)	> 0.05	8/103 (8 %)	6/115 (5 %)	> 0.05
Nonspecific	9/59	11/70		3/55	2/35		12/114	13/123	

Includes those positive ith serum 1 100.

TABLE 1_. Occurrence of antibodies to the patient own streptococci, studied with indirect fluorescence technique using FITC anti IgM. The results are expressed as the number f sera gi ing a positi reaction ith t least one strain, per umber f sera tested.

Fluorescence	Rheumatoid group I	Control group I	P	Rheumatoid group II	Control group II	P	Rheumatoid groups I+II	Control groups I+II	P
Positi e, serum 1 10	12/38 (32 %)	6/38 (16 %)	> 0.05	11/32 (34 %)	3/32 (9 %)	0.01	23/70 (33 %)	9/70 (13 %)	0.005
Positive, serum 1 100	4/38 (11 %)	3/38 (8 %)	> 0.05	3/32 (9 %)	2/32 (6 %)	> 0.05	7/70 (10 %)	5/70 (7 %)	> 0.05

Includes those positi with serum 1 100.

TABLE 13. Species distribution of streptococcal antibodies detected with FITC-anti IgG

Species	Rheumatoid groups I + II				Control groups I + II			
	Fluorescence Positive		Non-specific	Number of strains isolated	Fluorescence Positive		Non-specific	Number of strains isolated
	serum 1:10	serum 1:100			serum 1:10	serum 1:100		
S. pyogenes	—	—	1	1	1	—	—	1
S. agalactiae	3	2	—	3	6	5	—	
S. dysgalactiae	—	—	—	1	—	—	—	—
S. equisimilis	—	—	—	—	1	1	—	1
S. "large colony" group G			—		—	—	—	—
S. sanguis	—	—	—	1	—	—	—	1
S. haemolyticus group Q	—	—	—	2	—	—	—	1
S. MG	1	—	1	4	—	—	—	—
S. salivarius	5	1	1	15	5	—	2	16
S. mitis	19	6		39	17	5	4	63
S. mitis, lancefield variant	8	1		1	11	5		23
S. bovis	1	1	—	3		1	—	
S. faecalis	—	—	—	—	—	—	1	
Unidentified	1	1	—	3	*	—	1	7
Total	46	14	7	114	45	17	11	1?3

* Includes those positive with serum 1:100

TABLE 14. Species distribution of streptococcal antibodies detected with FITC-anti IgM

Species	Rheumatoid groups I + II				Control groups I + II			
	Fluorescence Positive		Non-specific	Number of strains isolated	Fluorescence Positive		Non-specific	Number of strains isolated
	serum 1:10	serum 1:100			serum 1:10*	serum 1:100		
S. pyogenes	—	—	1	1	—	—	1	1
S. agalactiae		1	—	3	1	1	1	7
S. dysgalactiae	—		—	1	—	—	—	—
S. equisimilis	—	—	—	—	—	—	—	1
S. "large colony" group G	1	1	—	2	—	—	—	—
S. sanguis	1	—	—	1	—	—	—	1
S. haemolyticus group Q	—	—	—	2	—	—	—	1
S. MG	3		1	4	—	—	—	—
S. salivarius	4	1		15		—	1	16
S. mitis	13	6	3	55	2	2	6	63
S. mitis lancefield variant	3	—	3	21	3			23
S. bovis	—	—	—	3	1	1	—	3
S. faecalis	—		—	—	—	—	1	2
Unidentified	—	—	—	3	—	—	1	7
Total	?7	8	1	114	10	4	13	123

* Includes those positive with serum 1:100

TABLE 15. Association of streptococcal antibodies in rheumatoid groups I + II detected with FITC-anti-IgG and FITC-anti-IgM to the latex reaction and Waaler Rose titre of each serum. The results are expressed as the number of sera giving positive reaction with at least one strain of the patient's own, per number of sera tested.

Fluorescence technique with	positive with	Latex reaction — +	Latex reaction ++ +++ ++++	P	Waaler Rose titre < 64	Waaler Rose titre > 64	P
Anti IgG	serum 1:10*	8/13 (62 %)	*7/37 (47 %)	> 0.05	9/26 (35 %)	26/44 (59 %)	> 0.05
	serum 1:100	5/13 (38 %)	5/37 (14 %)	> 0.05	3/26 (12 %)	10/44 (23 %)	> 0.05
Anti IgM	serum 1:10*	1/13 (8 %)	23/37 (39 %)	0.003	7/26 (27 %)	16/44 (36 %)	> 0.05
	serum 1:100	—/13	7/37 (12 %)	0.007	—/26	7/44 (16 %)	0.006

* Includes those positive with serum 1:100.

reaction ($P = 0.003$ with serum dilution 1:10).

The same tendency although not as obviously appears when the sera are classified according to the Waaler Rose titre. Positive reactions with FITC-anti IgG have no correlation to the Waaler Rose titre, whereas IgM antibodies found in serum 1:100 are all in the sera with a Waaler Rose titre of 128 or more.

Very few control patients had a clearly positive latex or Waaler Rose reaction, and it is not possible to compare the occurrence of the rheumatoid factor with the streptococcal antibodies in the control sera.

Cross-reactions of the antibodies detected by immunofluorescence

To test further the specificity of the antibodies detected by immunofluorescence technique all sera giving a positive reaction against at least one of the patient's own strains were tested against twelve strains isolated from the throat of control patients and giving negative immunofluorescence reactions with the patient's serum (Table 16). In the tests with FITC-anti IgG positive reactions per serum were obtained equally both in the rheumatoid and control groups, on average with a little more than two of the twelve strains used. With FITC-anti-IgM, rheumatoid sera gave almost twice as many positive reactions as the control sera ($P = 0.02$).

TABLE 16. Cross-reactions of the sera giving a positive indirect fluorescent staining with at least one strain of the patient's own. Each serum 1:10 was tested with twelve strains isolated from the control group and giving negative immunofluorescence reactions with the patient serum. FITC anti-IgG or FITC-anti-IgM or both were used with each serum, according to the immunoglobulin class of the antibody to the patient's strain. Figures in parentheses refer to the number of sera.

Fluorescence technique with	Positive reactions per serum Mean ± S.D. Rheumatoid groups I + II	Control groups I + II	P
Anti-IgG	_17 ± 0.71 (35)	_05 ± 0.91 (36)	> 0.05
Anti-IgM	_30 ± 1.40 (23)	1.33 ± 0.8 (9)	0.02

S. equisimilis, strain 85
S. sanguis, strain 53
S. haemolyticus, group Q strain 5_
S. salivarius, strain 45
S. salivarius, strain _3_
S. mitis, strain 41
S. mitis, strain 50
S. mitis, strain 56
S. mitis, strain 77
S. mitis (inactive variant) strain 56
S. faecalis, strain 4
Unidentified, strain 37

Comments on the methods

The methods used to study the physiological characteristics of streptococci are old and used in many laboratories. Every centre usually has its own combination of tests. Minor divergencies in the methods and media taken together with the general sensitivity and variability of streptococci readily lead to different results, and make the comparison between the results presented by different authors difficult. Even the most usual streptococci are often described by doubtful and equivocal characteristics (BROWN 1953). In the present work all strains were tested according to the same schema to facilitate the comparison between different species. SWIFT (1952) and BREED *et al.* (1957) emphasize that the identification of a given streptococcus must be performed by determining its complete physiological pattern. I have tried to study characteristics giving simple and reliable results useful in placing a strain into a species.

The ability to grow in 4 per cent and 6.5 per cent NaCl-broth, in broth with pH 9.6 and at 45 C are all in principle good tests. If all these reactions are positive, they indicate that the strain might belong to the enterococcus or lactic group. Streptococci of these two groups give good uniform growth in broth, while unfortunately most of the viridans streptococci show scanty often granular growth in broth. When, however very faint growth can occur surrounding the inoculum in such a medium, which does not allow general growth, it has been difficult to determine the growth characteristics of the viridans streptococci in many cases. This is reflected also in the results of these tests where a considerable number of viridans group strains were recorded as positive.

The use of litmus milk in the study of the streptococci is very old. Strong reducing action is typical of enterococci and lactic streptococci they reduce the dye before curdling the milk. In fact, reduction after the curdling may largely be the result of the milk itself (SHERMAN 1937). These two groups of streptococci can, however be recognized by their growth ability and their serological type. Hence in this work attention has not been paid to the order in which the acid formation, curdling and reduction have happened and the reaction has been recorded only once, after three days growth.

The ability to form ammonia was studied using peptone as substrate. The detection of ammonia is not very reliable because the negative control also gives a faint green colour and the difference in the intensity is to be estimated (SEELEMANN 1954). The test was used because it might be helpful to differentiate

some strains of *S. mitis* from *S. salivarius*. The results (Table 2) indicate that an error towards a positive tendency is common.

The fermentation of various carbohydrates and alcohols forms a set of proved bacteriological methods. The ability of streptococci to give varying results from time to time is a disturbing factor (SHERMAN 1937, SWIFT 1952, BREED *et al.* 1957, HALLMANN 1961). Many strains have however some typical and relatively constant fermentation reactions.

Most species outside the viridans group have a number of typical characteristics, the most important being the serological group. In this work, main attention was to be concentrated on the viridans group streptococci which do not belong to any Lancefield group and show a great variability in the biochemical reactions. To compensate this variability, quite a large number of different characteristics has been studied. The difficulties and differences in the identification of especially the viridans group streptococci make feasible that one centre can identify a strain belonging to the viridans group and another can place it among the pyogenic group streptococci (SHERMAN *et al.* 1943, SEELEMANN & OBIGER 1964). The confusion is not diminished by the disagreements concerning the nomenclature. I have followed the system proposed by SHERMAN (1937) and recommended by BREED *et al.* (1957). For example, in English literature the term *S. salivarius* is used but GUTHOF (1960) suggests the name *S. hominis* for this species. SEELEMANN again uses the name *S. salivarius* in his earlier articles (SEELEMANN & RABE 1948, SEELEMANN 1954) and divides this α-hemolytic streptococcus into five subtypes. Later he separates the nonhemolytic *S. salivarius* from the greening *S. viridans* dividing it into the same subtypes (SEELEMANN & OBIGER 1964). Obviously the earlier *S. salivarius* is the same as this *S. viridans* and SEELEMAN is of the opinion that this streptococcus is identical to the *S. mitis seu mitior*. The *S. viridans* of SEELEMANN corresponds rather well with the *S. mitis* in the present paper. The inactive variant of *S. mitis* does not correspond to any of the SEELEMANN's subtypes. The negative fermentation reactions and the growth characteristics distinguish it from *S. salivarius*, and the nonhemolysis or only weak greening on blood agar distinguish it from *S. mitis*. Similar strains have been found also by KORTEKANGAS (1959).

Because of the faint growth of streptococci it was possible to lose some species, especially in those samples having rich other than streptococcal flora. The poorly growing *S. mitis* could especially be in danger of being lost. The 399 isolates in the groups I which proved to be 129 different strains show that too many rather than too few colonies per each patient were tested.

As far as the antibody tests are concerned, the weak cross-reaction of FITC-anti IgM with IgG makes is possible that antibodies detected with this antiserum include also some of IgG class. There is, however, no reason to assume that the number of these cross-reactions should be different in the rheumatoid and control groups. The considerably

greater number of antibodies detected with anti IgG than with anti IgM reveals that the cross-reactions of the latter have been in practice very few

Streptococci isolated

The present results show clearly that the streptococcal flora in the throat of the patients with rheumatoid arthritis does not differ from that of control patients. The greatest number of the isolated strains belong to the viridans group generally considered avirulent. The small number of pyogenic group strains, ten in the rheumatoid groups and eleven in the control groups, is striking. The result does not correspond to that of FRANÇOIS (1965) who isolated streptococci of the pyogenic group in 31 out of 54 rheumatoid arthritis and in 21 out of 55 nonarthritic patients, and from these eight *S. pyogenes* in the rheumatoid group and two in the non-arthritic group. I have found only two *S. pyogenes* one in the rheumatoid and one in the control groups. The results concerning *S. agalactiae* are also interesting, especially when compared with those of SVARTZ (1938, 1960). She claimed to have found streptococci of this type in a high percentage of rheumatoid arthritis patients and considered its role in the disease very probable. From these strains, however, only three out of fifteen gave positive precipitation reaction against group B antiserum. She did not compare the occurrence of *S. agalactiae* in rheumatoid arthritis to that in non-arthritic patients. VENTERS & GOOD (1963) found no *S. agalactiae* and HOUBA *et al.* (1964) no hemolytic streptococci in the throat of patients with rheumatoid arthritis. In the present material the frequency of *S. agalactiae* is considerable but most of these strains were found in the control patients. Possibly the common use of milk in Scandinavia might explain the great number of these streptococci found by SVARTZ and myself. In the light of the present results, their role in rheumatoid arthritis seems negligible.

Polymorphism in the biochemical characteristics of the viridans group streptococci makes it attractive to search among them for a strain typical for rheumatoid arthritis. The streptococcus named an inactive variant of *S. mitis* differs from both *S. mitis* and *S. salivarius* and cannot be considered any other species. This variant was, however, prevalent equally in the rheumatoid and the control groups. Table 4 does not give the individual characteristics given by each strain but they did not reveal any streptococcal type characteristic for rheumatoid arthritis.

In rheumatic fever the streptococcal infection precedes the onset of the disease and at the time of developing joint symptoms *S. pyogenes* is not usually to be found in the throat of the patients. One might expect that the possible causative agent of rheumatoid arthritis also could be recoverable only before the clinical onset of the disease (CHRISTIAN 1964). The chronic character of rheumatoid arthritis and the constancy of rheumatoid factor during it speak against this. These facts suggest that the possible antigenic stimulation in the disease must be continuous (FUDENBERG &

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Supplementum 502

Long-term Cardiac Pacing

Experience of fixed-rate pacing with an endocardial electrode in 260 patients

By OLOF EDHAG

Distributed by The Almqvist & Wiksell Periodical Company

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LONG TERM CARDIAC PACING

Translated from the Swedish

by

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LONG-TERM CARDIAC PACING

Experience of fixed-rate pacing

with

an endocardial electrode

in 260 patients

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OLOF EDHAG

STOCKHOLM 1969

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PREFACE

The last decade has seen an enormous development in the field of cardiac pacing, and today this is a well established measure in certain kinds of arrhythmias. In Stockholm the implantation of permanent pacemaker units has been carried out at the Department of Thoracic Surgery Karolinska Hospital some of the examinations before supplying a pacemaker and most of the follow-ups of the patients have been performed at the Department of Medicine, Serafimer Hospital. The results and experience gained at these Departments, and particularly the latter from a consecutive series paced with endocardial electrodes have been analysed and are presented in this monograph. This series of patients with transvenous electrodes is larger than any that has been published hitherto at least with such a long mean observation period.

Haemodynamic examinations before and during triggered pacing, and some of the checks of the patients with atrial-triggered generators have been performed at the Institute of Thoracic Diseases, Karolinska Hospital. Studies of the haemodynamic influence of triggered pacing will be reported elsewhere.

An experimental study of the effect of digitalis on the ventricular automaticity was prompted by observations during the pacemaker follow-ups (routine checks of paced patients) and in view of the clinical significanse of the results an account of this study is included here. This study was performed in collaboration with Anders Rosén, M. D In another study included in this investigation namely *Rehabilitation of paced patients* Miss Eva Märta Wedelin was my co-worker

The publication of this report provides me with the opportunity of expressing my appreciation of the assistance received from many quarters in the course of this investigation.

The investigation was initiated by Professor Gunnar Biörck, who also gave support and advice throughout the course of the work. Bengt Pernow M. D critically examined the results of the ECG examinations and the experimental study Patient records at the Department of Thoracic Surgery Karolinska Hospital, were kindly placed at my disposal by Professor Viking Olov Björk.

Johan Landegren, M. D aroused my interest in the pacemaker field. Hans Lagergren, M. D was helpful in collecting the data concerning the surgical and technical complications and offered valuabl advice on this part of the study Erik Orinius, M. D has kept me going throughout the work, not least with stimulating discussions at various stages. Erik Berglund, M. D Juhani Paasikivi, M. D Bengt Thomasson, M. D and John Wahren, M. D have offered advice and criticism of the manuscript. Torbjörn Lundman, M. D has given advice in connection with calculations on computer IBM 7044. Most of the autopsies have been performed by Hans Nordenstam, M. D Other colleagues at and outside Serafimer Hospital provided data on the patients composing the material.

Assistance in the follow-up examination was given by Mrs Elsa Gillström-Eriksson. Advice on statistical matters has been re

ceived from Erlendur Larusson, fil. lic. The photographs were produced by Miss Marie-Louise Persson and Mr Bertil Wallerman. The figures were drawn by Mrs Viveka Sandberg, who together with Mrs Gunilla Haag also typed the manuscript.

I wish also to acknowledge grants from the Swedish National Association against Heart and Chest Diseases, the Martha and Gunnar Gordon Foundation, the Claes Groschinsky Foundation and the Folksam Insurance Company

CONTENTS

DEFINITIONS AND ABBREVIATIONS

Age — Notices about age are from the time the electrodes were inserted and the pacing started.

The first artificial electrical stimulation of the human heart is traditionally attributed to Burns[19[illegible]] in 1809 and Aldini[171] in 1819. A successful attempt to stimulate a heart that had stopped beating by applying an electric current was reported by Duchenne[19[illegible]] in 1870. The first electrical impulse generator for heart stimulation was probably designed in 1932 by Hyman[19[illegible]]. By applying electrodes to the chest over the heart Zoll[231] (1952) found that he could stimulate the heart when at ventricular standstill. Stimulation with epicardial electrodes was used in 1958 by Weirich, Paneth, Gott & Lillehei[222] after surgical damage had been caused to the atrioventricular conduction and in the same year in cases of permanent, complete heart block and arrhythmic syncope by Elmqvist & Senning[[illegible]]. The electrode wires were brought out through the thoracic wall at the level of the heart and connected to an externally worn battery-driven impulse generator. Pacing with a percutaneous electrode inserted to the myocardium was performed the same year by Thevenet, Hodges & Lillehei[215]. Because of complications such as cessation of stimulation due to loss of contact between the electrode and the myocardium, and rise in the stimulation threshold through fibrosis or infection around the wires the method was seldom effective for more than some weeks[227].

By using, instead of stainless steel[41, [illegible]] a more inert material for the electrodes, such as platinum[224] and platinum-iridium[43] the increase in threshold could be lessened. The electrode wires were made thinner and more flexible so as to reduce the risk of perforation. The advent of small transistorized generators for subcutaneous implantation[43, [illegible]] enabled them to be placed subcutaneously in the axilla or abdominal wall, thereby reducing the risk of infection along the wires.

In 1958 Furman & Robinson[73] described a catheter with a metal guide which could be inserted to the right ventricle through an arm vein or a jugular vein for endocardial pacing, thereby avoiding thoracotomy. In endocardial stimulation the transvenous electrode can be made unipolar: the stimulation electrode, the cathode, is then inserted to the endocardium while the indifferent electrode, the anode, is implanted subcutaneously[12[illegible]]. The indifferent electrode can also be applied to the wall of the impulse generator and then only one, unipolar electrode wire is needed[1[illegible]]. The endocardial electrode can also be made bipolar[43, 72, 170] with a common wire for the anode and cathode.

The use of endocardial electrode wires for pacing of the human heart over long periods has been attended by few serious complications[14, [illegible]].

The aim of the investigation which was conducted between February 1962, and March, 1968, was to ascertain the effectiveness of fixed rate pacing on the basis of an analysis of clinical data recorded in a pacemaker series during stimulation and to compare these findings with corresponding observations prior to pacing. An experimental study of the effect of digitalis on ventricular automaticity was prompted by the observation that in patients using this drug during pacing, the period elapsing before idioventricular activity was recovered was prolonged.

Surgical technique

The surgical method used has been described earlier[122, 126]. The pacing system used in the present series consisted of a unipolar electrode for endocardial stimulation and a subcutaneously implanted indifferent electrode, both of them connected to the impulse generator. The stimulating electrode is inserted through an external or internal jugular vein into the superior vena cava and advanced to the apical region of the right ventricle (Fig. 1). The electrode is lodged under the trabeculae in the apical region of the right ventricle (Fig. 2) and, after a few weeks of pacing, fixed by connective tissue to the endocardium (Fig. 3). Before ligating the electrode wire in the jugular vein and suturing it beneath the sternocleidomastoid and scalenus muscles the stimulating threshold is established; this is done by a method that had been used routinely since 1966.



Figure 1. The principle of stimulation, with the endocardial electrode tip located in the right ventricle and the indifferent electrode subcutaneously below the left costal arch. The impulse generator was first worn externally (1) and, after a few weeks pacing, implanted subcutaneously in the abdominal wall (2).

The indifferent electrode is implanted subcutaneously in the abdominal wall, usually below the left costal arch.

Pacemaker components

Electrodes. — Both the endocardial (transvenous) and the indifferent electrode wires (Fig. 4) consist of a Terylene core around which 4 very thin platinum strips are wound; the whole is enclosed in a polythene sheath. For the first 2 years (up till May 1964) a stimulating endocardial electrode tip of stainless steel was used, and thereafter a platinum-tipped transvenous electrode, with an area of 65 or 45 mm². The indifferent electrode terminates in a stainless steel disc, 20 mm in diameter (Fig. 4).

Fixed rate impulse generators. — The generators for fixed-rate stimulation are shown in figures 4 and 5. They were of the externally worn type (EM 138, Elema-Schönander)[81] or for subcutaneous implantation (EM 137, 139, 142)[81, 122].



F gure 2. An endocardial electrode in an ideal position in the right entricle after few days pacing

In 1965 the fixed rate generator EM 137 with 5 mercury cells was modified to the EM 139 also with 5 cells In both these types the voltage was about 6.5 The EM 142 which has been available since 1967 has 4 batteries, giving about 5 2 V The stimulation rate for these 3 models is about 70/min. The expected life of the generator is at least 2 years. For safety however, the generators were replaced routinely every 18 months.

Triggered imp lse gene ators are designed to stimulate chiefly when the sinus rhythm or A V block I is interrupted by severe heart block, or vice ersa[125] Two types of triggered generators have been used one for atrial-triggered pacing (EM 141) with a detector electrode implanted with the aid of mediastinoscopy behind the left atrium, and the other for entricular-triggered pacing (EM 143) where the endocardial electrode is used to pick up the R waves for triggering the generator and for myocardial stimulation.



F gure 3 An endocardial electrode wire in the right atrium and entricl after 4 years pacing; the tip is located in the apex of the entricle It is invested with connectiv tissue, by which it is attached to the wall (except at the place where it passes through the tricuspid orifice)

Atrial-triggered gene ator — The physiologically most appropriate type of generator is the atrial triggered one, which stimulates the right ventricle 0 10—0 12 s after the P wave. A detailed description of this type of generator has been given by Lagergren, Johansson, Karlof and Tornander[127] This generator has been recommended for use in young patients with conduction defects who live an active life[121] but its most important application is in the case of retrograde P activation and other arrhythmias with untoward haemodynamic sequelae[104 112] This type is contraindicated in A V block patients with atrial fibrillation or flutter or

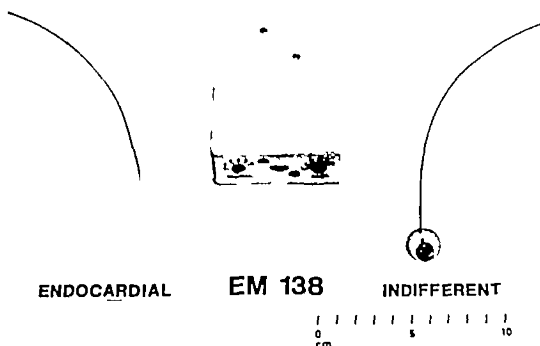


Figure 4. The externally worn impulse generator (EM 138), an indifferent and endocardial (stimulating) electrode are seen.

angina pectoris[202]. For patients with a marked tendency to develop atrial arrhythmias — for instance those with mitral stenosis, atrial septal defects, cardiomyopathies or severe heart muscle lesions of various origins — the atrial triggered generator is unsuitable.

Ventricular triggered generator. — If the ventricular rate is between 60 and 120 beats/min the R waves will trigger this type of generator to deliver impulses after a delay of only 10 ms in the absolute refractory period. Should the ventricular rate drop below 60 beats/min, the generator goes into fixed-rate pacing at that rate; if it exceeds 120 the generator develops a 2:1 block, while a further rise will produce a 3:1, 4:1 or higher block[89, 113]. In other words, the stimulation rate cannot exceed 120 impulses/min. The ventricular-triggered type is suitable mainly for patients with intermittent CHB, A-V block II with a slow ventricular rate, or extreme sinus bradycardia, and for those with frequent ventricular ectopic beats.

Impulse generators in use at the end of the observation period

At the end of the observation period (31st March, 1968) external fixed-rate impulse generators (EM 138) were being used by 33 per cent of the patients in the series (86/260), the implanted fixed-rate type (EM 139, 142) by 46 per cent (118/260), the atrial-triggered (EM 141) by 16 per cent (42/260) and the ventricular-triggered type

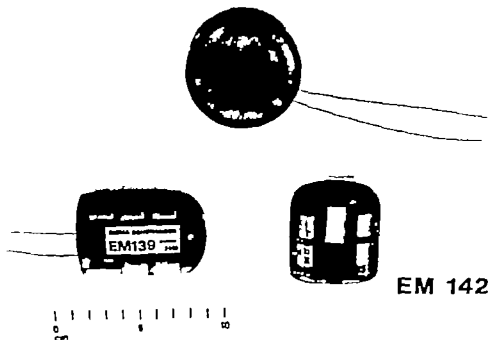


Figure 5 The subcutaneously implantable fixed rate impulse generators (EM 137 139 142)

(EM 143) by 5 per cent (14/260) Atrial-triggered pacing had been used for on average, 18.8 (±1 32) months, and ventricular triggered for 10 1 (±0 62)[1] months. The follow-up of the triggered impulse generators or the detector electrode in the case of atrial-triggered pacing is not included in this report.

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[1] Here and elsewhere, the figures following the means are the standard error of the mean.

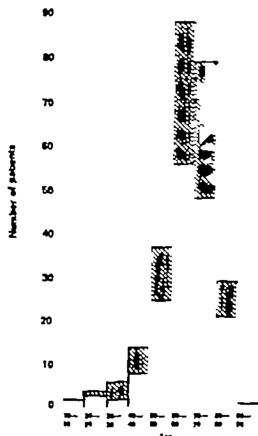


Figure 7. Age distribution of the 260 patients at the time the transvenous electrode was implanted. Filled bars denote men and hatched bars women.

defects, with or without arrhythmic syncope, or acute conduction defects that were expected to persist or recur. Two patients with recent myocardial infarction and acute CHB and one with CHB that appeared in connection with an operation for ventricular septal defect were not included; disturbances in the A-V conduction having these origins are usually temporary[133, 143].

METHOD FOR FOLLOW-UP

A follow-up examination was performed in the autumn of 1967 at the Department of Internal Medicine, Serafimer Hospital. The author interviewed and performed a clinical examination of all but 2 of the patients that were still using a pacemaker unit; the 2 exceptions, who were checked at other hospitals, were interviewed by telephone. The others were seen at the time of the pacemaker check-ups.

Possible causes of the arrhythmias and coexisting diseases. — Information on diseases that might give rise to conduction defects or conceivably have had a bearing on the results of the pacing was obtained from the patients' records and was supplemented at the follow-up examination (Section V).

Surgical complications. — The surgical reports and other records at the Department of Thoracic Surgery, Karolinska Hospital, where the implantations were performed, were examined for information relating to the reason for and time of any replacement or correction of the electrode wires and generators. In the cases in which the surgical reports or other records were not available at the Department of Thoracic Surgery the information on the surgical operation was obtained from notes kept at the Department of Internal Medicine, Serafimer Hospital, at routine out-patient checks or while the patient was admitted to that Department (Section VI).

Clinical observations before and during pacing. — In order to obtain an impression of the patients' clinical picture before the electrodes were implanted, their earlier medical records were checked.

At the follow-up examination the patient was questioned on the time elapsing from the onset of a slow pulse rate and/or from the first attack of arrhythmic syncope until the implantation of the electrodes. The number of attacks occurring before pacing was introduced was judged from the patient's and his relatives' recollection. The clinical

TABLE 1 Data relating to pacing for patients provided with an epicardial electrode (E) at the Department of Thoracic Surgery Karolinska Hospital

Epicardial electrode				Transvenous electrode		
Patient no.	Age at insertion	Duration of treatment (months)	Reason for change of electrode	Patient no.	Time treated (months)	Patient at end of study
E 1	69	32	electrode disconnected	10	70	alive
E 2	74	32		—	—	dead
E 3	75	55		—	—	dead
E 4	40	29	threshold raised	40	59	alive
E 5	57	16	electrode disconnected	18	46	dead
E 6	67	35	threshold raised+infection	59	49	alive
E 7	61	69	threshold raised+infection	223	2	dead
E 8	69	58	threshold raised+infection	146	26	alive
E 9	47	83		—	—	alive
E 10	55	11		—	—	dead
E 11	64	9	electrode disconnected+infection	3	1	dead
E 12	56	81		—	—	alive
E 13	21	1 week		—	—	dead
E 14	73	59	electrode disconnected	179	21	alive
E 15	56	24	threshold raised	46	55	alive
E 16	60	1 day		—	—	dead
E 17	74	78		—	—	alive
E 18	47	77		—	—	alive
E 19	46	73		—	—	alive
E 20	72	54		—	—	alive

picture during the circulatory arrest, including any injuries, was recorded on the basis of the patient's and eye-witness accounts. Note was made of the blood pressure recorded immediately prior to the implantation. If the patient was in a state of chock at that time, an earlier recording was listed. The indications for pacing were judged on the basis of the anamnestic and records data. *Any ECG findings prior to the pacing* were annotated. If more than a year had elapsed since the previous radiographic examination of the heart and lungs a new one was performed.

The reported observations on the heart and lung radiographs and EEG were obtained from routine examinations. Heart volumes were calculated from a radiograph exposed in the prone position [108, 109]. The occurrence of any pulmonary congestion was recorded. The patient was also questioned on whether during pacing, he had suffered from syncope, a feeling of arrhythmia or any annoying twitching around the indifferent electrode. Note was made of any relevant medication. The presence of heart *failure was assessed on the basis of anamnestic* data and the physical examination at the follow-up (Section VIII).

ECG analysis — The ECGs registered in attack free intervals before pacing were analyzed. Those taken during attacks were examined with respect to the type of arrhythmia. For this scrutiny records were

obtained from private practitioners, duty physicians and hospitals to which the patients had been admitted before the pacemaker unit was provided. The ECG during pacing was also analyzed. Note was taken of the rhythm during a short interruption in the pacing — if and when this could be safely made (Section IX).

Survival. — A comparison of the survival was made between the patients in the present series and those in some CHB materials, other pacemaker series, and in the general population (Section X).

Mode of death and autopsy findings. — The mode of death of the patients dying while using a pacemaker was analyzed. In most of these cases the whole pacemaker system was carefully examined. Autopsy findings that might have had a bearing on the fatal outcome and that were obtained from the autopsy reports are dealt with below (Section XI).

Clinical findings prior to death. — The clinical findings relating to the deceased were obtained from the records and the results of the follow-up examination. Where death preceded the follow-up examination the assessment was made only on the basis of the record data (Section XII).

Rehabilitation. — To obtain an impression of the users' attitude to the pacemaker units and the implications of this device as regards their social adaptation, 135 consecutive patients from the series were interviewed with the assistance of a welfare officer who recorded answers to standardized questions. Four patients that were using epicardial electrodes and that had been regularly followed at the Serafimer Hospital were also questioned. The periods that the interviewed patients had spent in hospital before and during the treatment were obtained from the General Health Insurance Offices (Section XIII).

Ventricular automaticity after digitalis. — From the author's observations recorded when a pacemaker generator was being exchanged it was found that when pacing was interrupted the period before idioventricular activity was resumed was longer for the patients taking digitalis than the others. This clinical observation of a depressive action of digitalis on the idioventricular activity was anticipated by the results of 2 preliminary studies[79, 85]. These findings prompted an experimental examination of the effect of digitalis on the ventricular automaticity (Section XIV).

Statistical methods. — The usual statistical methods presented by Snedecor[199] in 1956 were applied. The differences between the means of the measured variables were calculated and examined by Student's *t* test. The degree of significance was reported at the 5, 1 or 0.1 per cent level. The survival rate was estimated by the life-table method[49, 85]. The survival rate for the general population was calculated from the life tables for the period 1961—66 obtained from the National Central Bureau of Statistics, Stockholm.

V POSSIBLE CAUSES OF THE ARRHYTHMIAS CO-EXISTING DISEASES

The frequencies of the more common diseases considered to be possible causes of complete heart block in some materials and of the arrhythmias in some pacemaker series are given in table 2.

The observed diseases that may have resulted in conduction defects or have been of significance for the results of the pacing in this series are reported in table 3 Even though some of the patients had none of the disorders the total is greater than 100 per cent as some of the patients had more than one of them.

Coronary heart disease

A diagnosis of CHD was accepted when angina pectoris or myocardial infarction in accordance with the criteria given below[103] was found in the records. In some patients infarcts were found at autopsy (page 70)

A diagnosis of CHD was also made in the case of patients where total occlusion of the larger coronary arteries was disclosed by angiography shortly before or after the pacemaker was implanted, or where severe arteriosclerosis of the coronary arteries was found at autopsy

Angina pectoris was defined as central chest pains — whether or not they radiated to the arms or towards the jaws — that accompanied physical effort or mental agitation and disappeared or were alleviated within a few minutes when the patient rested or took a nitro drug Anginal pains in association with arrhythmias or dizziness were disregarded in the evaluation.

Myocardial infarction was recorded for the purpose of this study only when it had already been diagnosed by a physician. A new evaluation was performed on the basis of the available data it was based on the occurrence of central chest pains that persisted for at least 30 minutes, whether radiating or not, a temporary rise in the transaminase activity with a GOT level of more than 50 I U and above the GPT level, and the appearance of conduction defects (bundle branch block, A V block I or II or CHB) S-T elevation or a Q wave.

The evaluation of myocardial infarction was sometimes complicated by inadequate record data. In addition, some of the patients in the series had conduction defects before the suspected time of infarction. Some patients with frequent arrhythmic syncope displayed a rise in transaminase activity though there were no other reasons for suspecting myocardial infarction Where there were neither central chest pains nor an ECG pattern pointing to myocardial infarction the rise was interpreted as due to ischaemia of other organs than the heart, *e g* the liver Another feature that complicated the diagnosis of infarction is the marked T wave changes, which usually began to appear after only a few days of pacing, and which may have been interpreted as a sign of subendocardial infarction.

Some patients, randomly selected, underwent *coronary angiography* at the Department of Diagnostic Radiology either at the Serafimer Hospital or at the Institute of Thoracic Diseases, Karolinska Hospital.

TABLE The frequencies of certain diseases in CHB and pacemaker cases

	No. of patients	Coronary heart disease		Acute myocardial infarction		Hypertension		Rheumatic heart disease	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Campbell[35]	74	17	*23*			10	*14*	3	
Card[49]	130	15	*12*	35	*5*	10	*8*		
Ellis[64]	43	20	*47*						
Gilchrist[77]	46	28	*61*					4	
Graybiel[80]	7	47	*65*					8	*11*
Harris[82]	100			5		3		4	
Ide[89]	71	33	*46*	8	*11*			4	
Johansson[102]	204	24	*12*	62	*30*	12	*6*	9	*4*
Kamil[104]	24	9	*38*	3		9	*38*	1	
Kay[113]	100	43	*43*	9	*9*			3	
Kempf[114]	25	11	*44*	4				4	
Lawrence[124]	49	49	*100*						
Penton[153]	251	58	*23*	49	*20*	62	*5*	21	*8*
Rowe[164]	278	96	*35*	38	*14*	68	*4*	23	*8*
Winters[217]	20	19	*95*	1					
Wright[220]	90	42	*47*			1	*23*	7	*8*
Wyn[221]	90	47	*52*	4		3		7	*8*
Yuceoglu[222]	78	73	*94*					2	
Zion[223]	32	6	*19*	13	*40*			2	
Zoob[226]	51	8	*16*	4					

Only in the case of occlusion of main trunks of the coronary arteries, demonstrated before pacing, did coronary angiography provide a basis for the diagnosis of CHD

The postmortem diagnosis of CHD was made on the basis of histologically verified myocardial infarction or massive arteriosclerotic changes in the coronary vessels.

Coronary heart disease was diagnosed in 27 per cent (68/256) of the patients (Table 4) 60 per cent (41/68) were men and 40 per cent (27/68) women their respective mean ages were 70.9 (±1 3) and 68 4 (±1 3) years. Altogether 17 per cent (43/256) of the patients had angina pectoris.

A diagnosis of *myocardial infarction* was made in one patient after central chest pains lasting more than an hour 4 years before the first attack of arrhythmic syncope she was tended at home the first ECG registration one month after this incident showed bundle branch block. In 3 patients a diagnosis of myocardial infarction was made on the basis of the history and a rise in the transaminase level, and in one patient an elevated transaminase level and onset of conduction defects but no simultaneous signs of infection. Two patients had a typical history a rise in transaminase and ECG changes indicative of recent myocardial infarction in connection with the onset of complete heart block and arrhythmic syncope about months after infarction one of these patients probably had a post-myocardial infarction syndrome[34] with a feeling of oppression, pleural pain and a rise in ESR to 80 mm

Aortic valvular disease		Mitral valvular disease		Congenital CHB		Diphtheria		Unspecific infections		Digitalis	
No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
				10	*14*	0					
9	*7*	4		13	*10*			1		12	*9*
				2		1		2		8	*19*
				7	*15*	2		3			
				6	*8*	4					
3		1				11/62	*18*				
				9	*13*	0				12	*17*
				0		8	*4*	11	*5*	14	*7*
								1		0	
				20	*20*	2		1			
				1				4			
		1	*5*			41	*16*			27	*11*
11	*4*	9	*3*	17	*6*	17	*6*	3		16	*6*
				3		2					
						1		10	*11*		
								1			
										1	
3				1		0		1			

in 1 h. None of the 7 patients in the series for whom a diagnosis of CHD was made on the basis of angiographically visualized occlusive changes in the coronary arteries had a history of angina pectoris or clinical infarction as none of them died, autopsy findings are not available. In none of the patients were conduction defects found in connection with the acute myocardial infarction (p 16)

Myocardial infarction was confirmed histologically in 23 patients (p 70) Only one of them had a clinical picture of infarction *before* pacing. Another developed intensive central chest pains shortly before the fatal outcome. None of the others in whom myocardial infarction was verified histologically had clinical signs of myocardial infarction

TABLE 3 The frequency of some diseases having bearing on the causation of the treated arrhythmias or on the results of the pacing

	Proportion of patients	Per cent
Coronary heart disease	68/256	*27*
Diabetes	28/260	*11*
Diastolic hypertension	57/258	*22*
Congenital CHB	14/260	*5*
Familial conduction defects	9/260	*3*
Cardiomyopathy	8/260	*3*
Acute rheumatic fever	21/239	*9*
Scarlet fever	45/206	*22*
Valvular heart disease	22/260	*8*
Diphtheria	39/253	*15*
Rheumatoid arthritis	8/239	*3*
Non-specific myocarditis	11/230	*5*
Chronic uro-polyarthritis	10/260	*4*
Sarcoidosis	4/260	*2*
Gall-bladder disease	75/252	*30*

TABLE 4. Coronary heart disease in 68 patients

	No. of patients	Per cent
Angina pectoris only	26	38
Clinical diagnosis of myocardial infarction	6	9
Occlusive changes at coronary angiography	7	10
Diagnosed at autopsy	29	43
Total	68	100

before the fatal outcome. On the other hand, 10 out of the 3 with myocardial infarction so confirmed, and all 6 with severe arteriosclerosis of the coronary vessels and no evidence of myocardial infarction at autopsy had angina pectoris.

DISCUSSION

The presence of conduction defects may complicate the diagnosis of myocardial infarction. Patients of the present series that had severe bradycardia, in 24 of whom an ECG recorded less than 70 beats per minute (p. 59), sometimes experienced a marked feeling of oppression. As it cannot be ruled out that the symptoms were due to the extreme ventricular rates, high or low, and that they were misinterpreted as angina pectoris, were patients with anginoid symptoms solely in connection with a feeling of arrhythmia not included in the CHD group. On the other hand, angina pectoris occurs more seldom in cases of CHD with complete heart block than with A-V conduction[13, 103]. Painless myocardial infarction has also been found to be overrepresented among patients with CHB[167].

Even pronounced CHD need not, of course, give rise to conduction defects; however, although the incidence of cardiosclerosis in Sweden is lower than in most other European countries and in the United States[20–23], because of the high mean age of the series this disease was probably present in a large proportion of the patients. It is thus possible that undiagnosed CHD was present in some of the patients in the series. Whether this disease in turn gave rise to A-V blocks that prompted pacing is doubtful, for in the case of slowly progressing arteriosclerosis it is possible that the rich vascular supply of the ventricular septum, with its numerous anastomoses, serves as a protection against conduction disorders. In a series of 43 normal human hearts James & Burch[100] found that the interventricular septum received most of the arterial blood from the left anterior descending coronary artery. In the posterosuperior portion of the septum, however, the right coronary artery gave off a relatively large branch to a small zone of the ventricular septum in the vicinity of the atrioventricular node. Gross anastomoses were found within the septum between the right and left coronary arteries; because of these, for a definitive break in the conduction to occur there would probably need to be occlusion of both the right main coronary artery — or its posterior branch — and the left anterior descending coronary artery.

From the results of a histological study Lev[110] inferred that perhaps the most common cause of CHB is sclerosis of the cardiac skeleton with secondary damage of the atrioventricular system. From an autopsy study of 37 cases of CHB Lenègre & Moreau[135] concluded that coronary heart disease is a rare cause of A-V conduction defects. In 1967 Davies[42] found on the basis of an autopsy CHB material that no more than 15 per cent of the patients had coronary heart disease.

Gilchrist[77] found angina pectoris in 7 out of 46 patients with CHB — the same proportion as in the present series The frequency of coronary heart disease in the CHB materials and the pacemaker series in table 2 varies widely and is sometimes higher and sometimes lower than for the present series. However in most of the series CHB developing during acute myocardial infarction was included

Diabetes

A diagnosis of diabetes was made i this series when there was glucosuria combined with an elevated fasting glucose level above 100 mg/100 ml[87] With these criteria 10 per cent of the patients had diabetes (28/260) Four of them (3 women, 1 man) received insulin therapy their mean age was 62 years Seventeen received antidiabetic drugs and 7 were on a low-carbohydrate diet 8 were women and 16 men, with a mean age of 69 years Diabetes was diagnosed in 16 per cent of the patients with coronary heart disease (12/68) among whom it was thus not significantly more common than n the series as a whole.

DISCUSSION

A diabetes frequency of 3 per cent in a pacemaker series has been reported by Harris and co-workers[83] while Gadboys, Lukban & Litwak[78] found the much higher frequency of 23 per cent Rowe[184] found 8 per cent in a CHB material (11/134) while in a Swedish series of this disease Johansson[103] reported diabetes in 11 per cent (17/150) a figure that does not differ statistically from that for the present material. Twelve of the present patients had myocardial infarction. Diabetes was significantly more common among the patients in his material with myocardial infarction than in those with other kinds of CHD or an unknown causation ($P<0.01$) It cannot be ruled out that in some of the patients with diabetes in the present series there was occlusion of arterial branches to the septum without clinical signs of myocardial infarction.

The frequency of diabetes in a Swedish series of myocardial nfarction collected by Sievers[197] was 8.4 per cent, and in another published by Wahlberg[216] it was 8.8 per cent. Diabetes has been shown to be over represented in coronary heart disease[217] The fact that in the present series the frequency of diabetes was about the same as in materials with myocardial infarction may be taken as evidence that silent CHD may have been present.

Hypertension

The systolic blood pressure was, on average, 165 3 ($\pm$2.0) mmHg and the diastolic 84 6 ($\pm$0.98) mmHg. The proportion of patients with a resting diastolic pressure of at least 100 mmHg was 22 per cent (57/258) and of at least 110 mmHg, 9 per cent (24/258)

Hypertension was diagnosed in a varying percentage of the series in table 2 Doubt has been expressed by Harris *et al*[83] regarding the significance of hypertension for the occurrence of CHB

Congenital complete heart block

A diagnosis of congenital heart block was made in patients with a history of slow heart rate when they were less than 20 years of age and there was no history of disease that may have been responsible for acquired CHB. Heart block in combination with other manifestations of congenital heart disease,

even if they had existed since birth, were not included in this group

In the present series 14 patients fulfilled these criteria. Eleven of them had a QRS width of at least 0 12 seconds.

DISCUSSION

It cannot be ruled out that some patients of the present series in whom congenital CHB had been diagnosed had another undetected, cause of the conduction defect.

Michaelsson & Swiderski[155] estimated the incidence of congenital CHB to be one in 10—20 000 children. In less than one half of 244 selected cases of congenital heart block they found another congenital malformation 15 per cent of the series were subject to arrhythmic syncope Out of a reexamined series of 24 children with congenital heart disease collected in Göteborg by Carlgren[37] in 1941—50 there were 3 with congenital heart block, one of them probably with a small ventricular septal defect and the other 2 without signs of coexisting heart disease.

Campbell[38] suspected that congenital CHB is not rare but often overlooked because the ventricular rate is fairly rapid and the possibility of this diagnosis is not recognized

A supraventricular pattern of the QRS complexes has been regarded as an important feature in this condition[3, 100] Most of the patients with suspected congenital CHB in this series had a QRS width of at least 0 12 seconds.

Familial conduction defects

Nine of the patients had relatives with conduction defects that were manifested after the age of 50 years, with no simultaneous signs of valvular heart disease or asymmetric myocardial hypertrophy Two patients in the material were sibs and another was a cousin to them. Two others were cousins One patient had a sister who received a pacemaker at another Swedish hospital. Another had a brother who had attacks of arrhythmic syncope and registered cardiac arrests. The sister of one and the father of another patient died after the debut of heart disease with fainting

DISCUSSION

Of the few earlier published series of familial heart block unaccompanied by other signs of heart disease none has contained so many cases of severe heart block and arrhythmic syncope as the present one. In a report of a case of Stokes-Adams disease published in 1903 Osler[168] mentioned that many of the relatives had slow pulse rates. A brother and sister with congenital heart block were described by Aylward[4] in 19 8 In 1964 Nakamura[160] reported familial conduction defects in 6 out of 61 infants and children with complete heart block. In 1949 Hansen[91] gave an account of a brother and a sister with CHB both of whom were over 50 years of age at the onset of CHB and arrhythmic syncope he could suggest no definitive cause of their conduction defects.

The incidence of proven or suspected complete heart block, with or without arrhythmic syncope in relatives of 9 of the patients of the present series can hardly be ascribed solely to chance, as it has been estimated that no more than 450 new cases of chronic CHB occur in Sweden each year[183]

One possible explanation of the familial accumulation of complete heart block among the elderly in the present series is a familial deficiency in the arterial supply to the conduction system, as a result of which even quite moderate changes in the vessels might

well lead to interruption of the conduction system. As none of these patients was submitted to coronary arteriography or came to autopsy no analysis of this possibility could be made.

Hypertrophic and/or familial cardiomyopathy

Hypertrophic cardiomyopathy was diagnosed when muscular hypertrophy was demonstrated by cardioangiography at heart surgery or autopsy examination. The part of the heart most frequently affected was the septum. This group also included a patient that probably had congenital mitral insufficiency there was also an unexplained sudden death of a young relative. The diagnostic features of hypertrophic and familial cardiomyopathy have been presented by Godwin, Gordon, Hollman & Bishop[79] and by several Swedish authors[12, 17, 21, 87, 186].

This diagnosis was made in 7 patients of the present material, in 5 of whom cardioangiography disclosed asymmetrical hypertrophy 2 of the 5 were also operated upon in one case suspected hypertrophy was verified at autopsy. Five of the group had a familial history of sudden death among young relatives. In the 2 patients operated upon, CHB had been present prior to cardiac surgery and in both of them subaortic muscle tissue was resected. One of the patients had mitral insufficiency without having had a rheumatic fever his father had died suddenly and inexplicably at the age of 35. He was the only patient in this group with no evidence of *obstructive* cardiomyopathy. The mean age of the 7 patients of the group at the time pacing was started was 37.5 years.

The literature contains a number of reports on familial or isolated hypertrophic cardiomyopathy with heart block[21, 79].

Previous acute rheumatic fever

A diagnosis of acute rheumatic fever was made when the patient was admitted to hospital for this disease or had a history of acute polyarthritis and fever that had led to confinement to bed for at least 3 weeks[88, 107].

The frequency of acute rheumatic fever without valvular involvement was 5 per cent (11/239) in 4 of these cases there was chorea. The patients with valvular engagement are described on page 26. In 3 cases the rheumatic heart disease coincided with the onset of the conduction defects. In one of them that had had acute rheumatic fever there was pericardial friction murmur.

DISCUSSION

In acute rheumatic fever atrioventricular conduction defects are not uncommon. Levander Lindgren[141] reported A V block I or II or CHB in 27 out of 38 patients with signs of myocarditis during the acute phase of rheumatic fever. In 5 of 24 patients in this group followed up for more than 6 months after discharge from hospital heart block was found. Bengtsson & Lamberger[10] found bundle branch block at a follow-up carried out 5 years after discharge in 4 out of 18 patients with rheumatic fever and signs of myocarditis during their stay in hospital. No complete heart block or A V block II was recorded in 6000 followed-up patients with rheumatic fever comprising an American material[86]. A V block I was, however, found in 325 of them.

Although acute rheumatic fever coincided with the discovery of conduction defects in no more than 3 patients of the present series, it is not improbable that there was a causal connection in more of them.

Scarlet fever

Twenty two per cent of the patients (45/206) stated, probably reliably that they had had scarlet fever In the acute stage of this disease there is sometimes a prolonged A V conduction[221] and cases of the development of CHB during the period of infection have been reported[14, 172] Levander Lindgren[111] found A V conduction disturbances in 3 out of 16 patients with acute beta haemolytic streptococcal infections Bengtsson et al[19] reported a case of conduction defect found at a follow-up of 20 patients 5 years after admission to hospital for myocarditis scarlatinosa. Among 71 patients with complete heart block Ide[89] found 2 cases of scarlet fever at the onset of the block.

Diphtheria

The diagnosis of diphtheria was accepted only in patients where the presence of this disease had been definitely established. Fifteen per cent (39/253) stated that they had had d phtheria.

DISCUSSION

In a review of the literature in 1925 Marin[149] found toxic myocarditis to be common during the acute course of diphtheria. Out of 13 patients where diphtheria had led to death he found complete heart block in 3 and bundle branch block in 5 Butler & Levine[32] found that there had been diphtheria in childhood in 10 out of 20 patients with A V block but not CHD and where there had been no digitalis medication, history of rheumatic fever or infection at onset. In 6 per cent of a control group of 600 patients n a surgical department he found d phther a The authors concluded that diphther a n hildhood may result in heart block in later l fe On the other hand, Jones & White[98] found no case of CHB among 100 patients examined more than 5 years after diphtheria.

The frequency of diphtheria among the pacemaker and CHB series in table 2 varies widely For instance Harris et al[82] and Penton[173] found diphtheria in 18 per cent of their materials, while Campbell[33] did not report any cases of this d sease. Six per cent (4/61) of the patients in Johansson s material[103] with CHB of unknown cause and 3 per cent (4/140) of those with some other conceivable cause also had diphtheria this difference is not statistically significant In Penton s series of CHB[173] on the other hand diphtheria was overrepresented in the group with unknown cause with a frequency of 7 out of 18 in this compared with 33 out of 206 comprising the group with other possible causes

Valvular heart disease

Rheumatic heart disease was diagnosed on the criteria given by the New York Heart Association[141, 48] Furthermore, patients with uropolyarthritis and aortic insufficiency were included in the valvular heart disease group Doubtful cases were discarded unless heart catheterization or phonocardiography bore out the clinical suspicion of valvular heart disease

Rheumatic heart disease and aortic insufficiency in association with uropolyarthritis occurred in altogether 8 per cent of the material (22/260) (Table 5)

There were 7 cases of aortic stenosis of them in combination with aortic insufficiency Altogether 11 patients had aortic insufficiency) In one of them a bicuspid aortic valve and chronic endocarditis were found at autopsy in 2, the aortic insufficiency was accompanied by aortic stenosis, in one by mitral stenosis and in another by

mitral insufficiency. Two of the 16 patients with aortic valvular disease were women. Aortic insufficiency was diagnosed in 3 of those with uropolyarthritis (p. 29).

There were altogether 4 cases of *mitral stenosis* which in one of them was combined with aortic insufficiency and in another with mitral insufficiency. In one of the cases of mitral stenosis commissurotomy had been performed.

There were 5 cases of *mitral insufficiency*. Of the 8 patients with mitral disease 2 also had aortic valve involvement. 5 of them were men and 3 women.

A diagnosis of clinical valvular heart disease was verified in 5 cases at autopsy. It was made in 7 patients on the basis of the results of heart catheterization or angiocardiography and in 8 by auscultation and/or phonocardiography in combination with heart radiography. Of these 8 patients 6 had aortic insufficiency, one mitral stenosis and one classical auscultatory findings of mitral insufficiency following rheumatic fever. In 2 patients the diagnosis made by heart catheterization was confirmed at heart surgery.

Ten patients with valvular heart disease had had rheumatic fever and 2 had had scarlet fever, while 5 gave no history of rheumatic fever, scarlet fever or uropolyarthritis. For 2 no information was obtainable.

DISCUSSION

In the case series in table 2 the frequency of rheumatic heart disease varies widely. In these reports the aortic valve was the one most often affected, but in the series of Rowe & White[181] the mitral involvement was almost as common. Segal[182] reported 9 cases of heart block among 191 patients with bacterial endocarditis submitted to autopsy.

TABLE 3. Valvular heart disease. 22 patients

	No. of patients
Aortic insufficiency	7
Aortic stenosis	5
Combined aortic valvular disease	2
Mitral insufficiency	3
Mitral stenosis	2
Combined mitral valvular disease	1
Aortic insufficiency and mitral valvular disease	2
Total	22

Partain & Sydnor[173] have stressed the importance of a correct diagnosis in patients with aortic stenosis and CHB associated with arrhythmic syncope.

Thickening of the aortic valve cusp

Thickening of the aortic valve leaflets, *with or without calcified atheromatous* changes, was found at autopsy or suspected on grounds of a systolic murmur of at least grade 2[183] over the second right intercostal space, often also heard along the left sternal margin towards the apex during pacing and with a retained second heart sound over the second *intercostal* space.

Thickening of the aortic valve cusp was found or suspected in 10 per cent (26/260) of the series.

The above observations have been found to be common in persons past middle age[30]. They have not been reported in any of the series *in* table 2. Their *bearing on the occur*rence of conduction defects is not clear.

Calcification of the mitral annulus fibrosus

This condition was an incidental finding at routine radiography in 2 patients. As no systematic fluoroscopy was performed in this

during mediastinoscopy performed in connection with application of the atrial detector electrode microscopic examination disclosed sarcoidosis The other 3 patients had radiographically visualized lung alterations

DISCUSSION

In about 20 per cent of the cases of general sarcoidosis in 3 autopsy materials the heart was involved[28, 78, 115] Arrhythmic syncope was observed in 14 out of the 29 patients of a sarcoidosis series in which this condition was found at autopsy to have involved the heart[174] In another series[177] comprising 53 autopsied cases of sarcoidosis 23 per cent had arrhythmic syncope or had died suddenly There are several earlier reports of conduction defects in sarcoidosis, some with arrhythmic syncope where pacing was introduced[101, 107, 176, 184]

Digitalis

The patients using digitalis at the onset of the conduction disturbances constituted 34 per cent (87/260) of the whole material In 52 per cent (45/87) of these the A V block disappeared initially after the therapy had been discontinued but recurred later on. In the other 48 per cent (42/87) pacing was begun while the digitalis therapy was being continued or before the effect of the digitalis had waned These patients either had such severe heart failure that continuous digitalis therapy was considered inevitable or they had such prolonged or frequent arrhythmic syncope that it was deemed unwise to postpone pacing until the effect of the digitalis had diminished

DISCUSSION

That conduction defects may appear even during maintenance doses of digitalis has been shown by among others Eckerstrom & Nordqvist[57] The patients in their material were all over 65 years, as were most of the patients in the present series In the series reported in table 2 digitalis therapy was regarded as the cause of A V block in 6—19 per cent of the patients

After digitalis therapy had been withdrawn in a patient with rheumatoid arthritis and CHB reported by Hoffman & Leight[94] A V block I developed In some patients of the present series conduction disturbances regressed after digitalis had been withdrawn but later on they recurred It would thus seem as if asymptomatic damage to the atrioventricular system may through digitalis therapy develop into a higher degree of heart block, sometimes with arrhythmic syncope Moreover the original lesion in the conduction system sometimes appears to have developed into symptomatic A V block later on without further digitalis therapy Patients with A V block II or CHB apparently induced by digitalis should thus be observed also after withdrawal of digitalis and regression of the conduction disturbances as the block may recur

Quinidine or procainamide therapy

Altogether 11 per cent (21/199) of the patients were receiving quinidine sulphate or procainamide at the time of onset of CHB or arrhythmic syncope 17 and 4 respectively

The indications for this therapy were ventricular ectopic beats in 10 cases together with A V block II or CHB, in 3 cases with atrial fibrillation, and in 2 with sinus rhythm. Out of 15 of these patients the ECG showed PVTA in 6. Atrial fibrillation alone prompted therapy in one and paroxysmal tachycardia in another patient In the

TABLE 7 Disorder of the thyroid gland in the material

Age	Sex	Disorder of the thyroid gland	Other diseases	Therapy
65	♀	thyrotoxicosis and adenoma of the thyroid gland	hypercalcaemia	carbimazol + ^{131}I
62	♀	thyrotoxicosis and goitre		thiouracil
72	♀	adenoma of the thyroid gland	uraemia and CHD*	none
72	♂	hyperthyreosis?	syphilis and pulmonary tuberculosis	^{131}I treatment 1 year after A V block
70	♀	goitre	rheumatic fever and CHD*	strumectomy 19 years before A V block
63	♀	adenomas of the thyroid gland	CHD* and gall-bladder disease	none
60	♀	goitre	rheumatic fever and diphtheria	strumectomy 39 years before A V block
55	♀	goitre		extract from thyroid gland for 1 year before A V block
51	♂	goitre	renal calculus	strumectomy 22 years after A-V block
37	♀	goitre	A-V block at 19 years congenital?	strumectomy 22 years after A-V block
35	♀	adenoma of the thyroid gland	obstructive cardiomyopathy and rheumatic fever	none

*CHD coronary heart disease

other 4 the indications for the treatment had not been recorded. In the case of one of the patients with atrial fibrillation and ventricular ectopic beats for which quinidine was given, PVTA appeared after conversion with a DC shock but recurred the next day on withdrawal of the drug. The patient was also taking digitalis. Altogether 15 out of the 21 patients in this group were taking digitalis before pacing was begun, and 7 of them up to the introduction of pacing

In 8 of the patients receiving quinidine sulphate or procainamide the onset of arrhythmic syncope coincided with the introduction of this therapy

DISCUSSION

Arrhythmic syncope has been reported earlier in patients with conduction defects who were taking quinidine or procainamide[117, 154, 180, 190] Gilchrist[77] and Zion & Bradlow[233] each reported one case of CHB which developed during quinidine therapy These drugs are contraindicated in patients with heart blocks without a pacemaker

Disorders of the thyroid gland

The patients with known disorders of the thyroid gland in the series are reported in table 7 In most of them there was appar

ently no association between the onset of the conduction defects and the thyroid condition. In the 2 cases reported below however there is possibly an association.

Case 99 — A woman aged 63 years with acromegaly and a large thyroid adenoma was admitted to the Department of Endocrinology Karolinska Hospital with thyrotoxic crisis. On her arrival the following values were recorded PBI 14.5 gamma per 100 ml, BMR +61 per cent, ^{131}I release 65 per cent in 4 h and serum calcium 11.6 mg/100 ml. A thyrostatic drug (carbimazol) was given for one month and followed by radioiodine. Four days later complete heart block and ventricular systole occurred, and a pacemaker was inserted. No digitalis had been taken. After 2 years a regular sinus rhythm was recorded on a number of occasions. She was then euthyroid.

Case 220 — A woman of 62 years with onset of finger tremor and sweating in 1959. A diffuse goitre was palpated. In 1960 toxic goitre was diagnosed. A thyrostatic (thiouracil) was given for one year. In 1961 complete heart block and arrhythmic syncope developed. At this time PBI was 4.2 gamma/100 ml and BMR +3 per cent. She had never taken digitalis. In 1966 a pacemaker was provided and at an examination one year later sinus rhythm was registered.

DISCUSSION

The first report of thyrotoxicosis with A V block and arrhythmic syncope have been published in 1882 by Merklen[183]. In 2 other reports[118, 204] the sinus rhythm recurred after treatment; in one of them[118] the onset of conduction defect was preceded by irradiation of the thyroid gland.

An A V block I was found in 1927 by Goodall & Rogers[78] in 242 out of 787 cases of thyrotoxicosis. On the basis of their observations these authors coined the term thyrotoxic myocarditis. No detailed analysis of these patients was conducted, however.

Possible causes of conduction disorders in thyroid disorders are following pressure exerted on the vagus nerve by an enlarged thyroid gland an adenoma or post-thyroidectomy scar tissue, with reflex disturbance of the sinus node or the A V conduction system, or a hormonal effect of the thyroid gland on the mesenchymal tissue of the heart. It is conceivable that this tissue might be affected by thyrotropin-stimulated swelling of connective tissue after thyroidectomy or radioiodine therapy? Treatment for thyroid disorders might conceivably result in secondary damage to the Purkinje cells of the heart. A myopathy that affects the heart muscle similar in type to that recorded on EMGs in diabetes and also hyperthyreosis is another possible cause. In the above 2 cases the most likely explanation would seem to be swelling of connective tissue elicited by thyrotropin.

Hyperparathyroidism

Hyperparathyroidism was diagnosed in 2 patients of the series.

Case 183 — A man of 33 years. He had recurrent renal calculus at the age of about 30 years at 44 ankylosing spondylitis was diagnosed, and 5 years later a parathyroid adenoma was removed (serum calcium 14.0 mg/100 ml). The next year there was complete heart block, and after a further 2 years arrhythmic syncope. A pacemaker was inserted when he was 54. At follow-up after 6 months of pacing, there was still CHB.

Case 45 — A man aged 69 with 2 cousins who also received pacemakers after attacks of arrhythmic syncope. In connection with treatment for stones in the ureter palpation disclosed a parathyroid adenoma. An ECG then showed the presence of A V block I and periods of sinus arrest, which periods were abolished temporarily by intravenous administration of methylscopolamine. Because of frequent attacks of arrhythmic syncope a pacemaker was supplied. The adenoma was removed subsequently.

DISCUSSION

It was found by Berliner[17] in 1936 that a rapid intravenous injection of calcium given to a subject with a sound heart can produce

sinus bradycardia, sinus arrest and unconsciousness. In 1960 Crum & Till[47] reported a case of hyperparathyroidism with the Wenckebach phenomena, which could be abolished by atropinization. In 1967 Voss & Drake[229] reported a case of parathyroid adenoma where there were attacks of dizziness. The ECG showed sinus rhythm, periods of sinus arrest and A V block I By injecting atropine the periods of sinus arrest could be eliminated. After a pacemaker had been implanted a parathyroid adenoma was excised For the next 11 months a sinus rhythm was registered

In the former of the above 2 cases the conduction defect may just as well have been due to uropolyarthritis as to parathyroid adenoma. In the second case it is not improbable that the parathyroid adenoma had a bearing on the appearance of the sinus arrest. This type of arrhythmia is identical with that in the case reported by Voss & Drake[229] furthermore, the arrhythmia could be eliminated by atropine. The clinical picture is obscured by gall-bladder disease, which can sometimes give rise to arrhythmic syncope[103]

Gall-stones

The patients with radiologically verified gall-stones or that had undergone cholecystectomy prior to the onset of the conduction defects constituted 30 per cent of the series (75/252) Twenty-eight per cent (35/126) of these patients with CHD myocarditis hereditary cardiomyopathy valvular or subvalvular heart disease, sarcoidosis or uropolyarthritis had gall-bladder disease compared with 32 per cent for the rest of the material (40/126)

In one case there was an association between the occurrence of arrythmic syncope and gall-bladder disease.

Cas 46 — A man aged 56 with uropolyarthritis, complete heart block and arrythmic syncope. After cholecystectomy the syncope ceased but the CHB persisted. Because of slow ventricular rate with low physical capacity pacing was introduced th was 7 years after cholecystectomy

DISCUSSION

In a CHB series Johansson[103] found gall bladder disease in 25 per cent (16/64) of those in whom the cause was unknown, against 11 per cent (15/140) of the rest of the material thus difference is statistically significant ($P<0.01$) There was no evidence of an elevated frequency of gall bladder disease among the patients in whom the cause of the arrhythmia was not established

In 1955 Maclemore, Jr & Levine[147] reported 7 patients with gall-bladder disease and arrhythmic syncope, which in 3 of them disappeared after cholecystectomy and in the others decreased in frequency In 1960 Johansson[103] reported a patient with arrhythmic syncope which disappeared after cholecystectomy

As cholecystography was not performed in all the patients of the series, nor was cholecystectomy systematically done in those with gall-stones, the importance of gall bladder disease for the occurrence of conduction defects is difficult to assess from this material.

Tuberculosis

Twelve per cent (23/189) of the patients in this series had had pulmonary tuberculosis.

Tubercles of the myocardium in the adult heart appear to be a rare occurrence, but there are reports of some cases in which tuberculosis was considered to give rise to complete heart block[48 77 87 182]

,

Other diseases

One of the patients of this series (for case history see p 72) had *metastases in the sinus node and the bundle of His from carcinoma of the small intestine* Metastases from, for example, bronchial and renal carcinoma have been regarded as being the cause of conduction defects[illegible] No previous reports of metastases to the myocardium in carcinoma have been found On the other hand in an examination of an autopsy series of heart metastases Berge & Sievers[11] found one case of carcinoma of the small intestine with such metastases

In one of the patients of the present series *dystrophia myotonica* was found[illegible] a diagnosis that was subsequently confirmed at autopsy

Another patient (case history p 72) had *a granulomatous tumour* with numerous eosinophile leukocytes in the A V node[illegible] and one of the same type in the hypophysis

A diagnosis of *Paget's disease* was made on the basis of radiologic findings in one of the patients in the following series. Earlier authors[illegible] have reported the occurrence of complete heart block in this disease and considered that there could be some association.

Ethylism — In 12 per cent of the series (30/260) there was a history of daily consumption of spirits or institutional treatment for alcoholism. Thirteen of these 30 patients also had a history or presented evidence of some other disease that has been considered to be capable of producing conduction disturbances.

In 1966 Alexander[1] reported 4 cases of complete heart block, 2 of A V block II and 16 of A V block I in a group of 100 chronic alcoholics Ethylism has also been reported in a few patients in CHB series[illegible]

General discussion

The comparisons as regards causative factors in this series have been made largely with CHB series. The complete heart block and the pacemaker series differ slightly in composition Some patients with complete heart block die in connection with one of their first attacks of arrhythmic syncope and do not appear in pacemaker series. Johansson[illegible] found that the outcome for patients with complete heart block was the same whether or not there was arrhythmic syncope ($P > 0.05$) Moreover there are conduction defects that may regress before pacing can be started examples are A V block induced by digitalis — which disappeared after withdrawal of the drug — or affected by steroid therapy in LED by uropolyarthritis or by thyroid extract in hypothyroidism. The conduction defects that appear during the acute phase of a myocardial infarction also usually regress In vagus-induced conduction defects due to gall bladder disease arrhythmias have also been eliminated by cholecystectomy[illegible] Pacing has also been used for other patients than those with complete heart block with or without syncope[illegible] Pacemaker stimulation has proved beneficial in PVTA unaccompanied by A V block. Prior to pacing, some patients of the present series registered sinus rhythm with paroxysmal ventricular tachycardia or sinus bradycardia without an A V block (p 57)

The development of bundle branch block or A V block I to complete heart block, possibly with arrhythmic syncope, sometimes takes many years (p. 57) As the pathologic condition primarily responsible for the damage to the atrioventricular system need not have elicited symptoms in the acute stage, it is often difficult to analyze the cause, as is underlined by the highly varying fre

quency figures for the various causes reported in the above materials (Table 2)

Some of the diseases that may have been of significance for the occurrence of the treated arrhythmias had special features, such as the manner in which the total block developed in uropolyarthritis (p 59) the type of arrhythmia in hyperparathyroidism, the restitution of conduction disturbances in hyperthyroidism, and recurrence of A V block that disappeared when digitalis was withdrawn but subsequently re-appeared.

Some of the diseases mentioned in this section appear to have been of significance for unsuccessful pacing they include hypertrophic cardiomyopathies and CHD and possibly aortic valvular heart disease (p 78)

VI. SURGICAL AND TECHNICAL COMPLICATIONS

The occurrence of certain surgical complications in the present series have been reported earlier[122, 128, 129, 131, 180]. Reports of complications in long-term endocardial pacing have been issued also from other departments[14, 51, 72, 81, 82, 100, 222].

IMMEDIATE COMPLICATIONS

In 1966 one patient died during the implantation of the endocardial electrode. In this case the heart wall was perforated by a steel guide used to get the electrode wire into position.

Case 169. — A woman aged 62, in good health apart from mild joint symptoms. Suddenly afflicted with severe respiratory distress she was admitted to hospital. Complete heart block was diagnosed, with a heart rate of 15 beats/min and a systolic blood pressure of 90 mmHg. She was transferred to the Department of Thoracic Surgery, Karolinska Hospital, in a poor state though without having fainted. An attempt was made to place an electrode wire in the apical region of the right ventricle, and because of difficulty in getting it into an acceptable position a steel guide was used.

When the electrode had eventually been satisfactorily placed in this way and the surgeon had begun to withdraw the guide there was respiratory and cardiac arrest. There was no response to pacemaker stimuli. Heart massage was begun without the guide having been fully withdrawn. Infused isoprenaline had no effect on the ventricular activity and artificial respiration was in vain. Autopsy disclosed a perforation of the myocardium about 3 mm across and the presence of about 500 ml of blood within the pericardium; the valves and coronary arteries displayed no appreciable changes. Microscopic examination disclosed a few inflammatory cells in the heart muscle.

Since that time a metal guide has not been used.

In one patient with frequent arrhythmic syncope during positioning of the endocardial electrode a plexus lesion was caused during the operation, which resulted in temporary paralysis of the right arm. No other serious injuries occurred during implantation of the electrode wire.

HEART PERFORATION, THROMBOSIS, TRICUSPID INSUFFICIENCY

In no case were there any clinical or radiographic signs that the electrode had perforated the right ventricle apart from the one described above (no. 169), nor was there perforation or incipient perforation in any of the patients submitted to autopsy examination. No clinical evidence of thrombosis around the transvenous electrode was found, nor were there any emboli. In 2 patients, however, thrombosis was found around the transvenous electrode wire at autopsy.

In one patient excess wire was fed into the right side of the heart, with tricuspid insufficiency as a result. This patient died from heart failure 2 months after the electrode implantation.

In 11 patients 2 endocardial electrodes were located in the tricuspid ostium (p. 39). There was no sign of tricuspid insufficiency in any of them.

EXCHANGE, REMOVAL AND REPLACEMENT OF THE ENDOCARDIAL ELECTRODE

At the end of the observation time the aggregate period of stimulation in all the patients was 567.5 years. In 31 per cent of

TABLE 8 Patients alive after 1—6 year of pacing and the number of them whose endocardial electrod had not been exchanged or corrected

Observation time (years)	1	2	3	4	5	6
Pacemaker in use						
Total	186	108	61	36	20	2
No change or correction of electrod						
Number of patients	134	71	33	15	6	0
Per cent	72	66	54	42	30	

the series (80/260) there was some kind of trouble with the endocardial electrode that necessitated its replacement or correction or was a factor in the decision to terminate pacing, 7 patients (Section VII) or that was discovered at autopsy 6 patients (Section XI) the mean age was 62 years Among the patients in which the electrode wire was replaced removed or corrected, or where it proved at autopsy to be defective or malplaced, the men (62) significantly outnumbered the women (18) ($P<0.01$) The mean age of the men for whom there was some malfunction of the wire, 60 3 ($\pm$2 1) was lower than the mean for the men of the whole series ($P<0$ 05)

Among the 80 patients where the endocardial electrode was replaced or its position was corrected or where it was found to be defective or dislodged at autopsy there were 56 with one, 18 with two, 4 with three and 2 with four non functioning wires. Instances of complications with the transvenous electrode numbered 112

Of the 260 patients comprising the series, 186 (72 per cent) were living and still being paced at the end of the follow-up period all had been observed for at least 12 months In 72 per cent (134/186) no change or correction of the endocardial electrode was required. The corresponding figures for the patients followed up for at least 2—6 years are given in table 8

Causes for malfunction of the endocardial electrode are given in table 9

The most common malfunction of the electrode was dislodgement the next in frequency was a rise in the stimulation threshold which led to intermittent or ineffective pacing An unsatisfactory position, with or without ineffective pacing, was another reason for exchanging the electrode. This group included patients in whom the electrodes were provided in an emergency and a check later on showed that the wire was stretched or that too long a portion had been fed in, with the result that loops formed in the right ventricle or atrium. In

TABLE 9 Sources and numbers of complications involving the endocardial electrod 260 patients

	No. of complications	No. of patients
Dislodgement	56	45
Unsuitable position	11	11
Threshold elevation	22	19
Infection	10	10
Defective insulation	6	5
Other known reasons	4	4
Unknown reasons	3	3
Total	112	

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At the end of the observation time the aggregate period of stimulation in all the patients was 567.5 years. In 31 per cent of

examinations performed near the time of the implantation, was the same for the group with wire dislodgement as for the whole material — 545 (±25) ml against 545 (±10) ml/sq m of body surface area.

At the time of the displacement 73 per cent (41/56) of these patients wore external generators. In 2 of the 4 in whom there was dislodgement of a transvenous electrode and who still were using an external generator at the end of the observation period there was a further displacement. These occurred 14 and 12 months after the wire had been re-implanted.

For the 17 with subcutaneous generators at the time of displacement the interval elapsing from the implantation to the first dislodgement ranged from 2 days to 15 months — mean 3 9 (±1.2) months. The corresponding value for the patients with external generators at the time of the first displacement was 3.9 (±1 7) months.

In 8 patients a fixed-rate impulse generator was implanted at the same time as the electrodes. In none of these was the endocardial electrode displaced The number is too small to show up any statistical difference in the frequency of dislodgement between the patients with externally worn and those initially provided with implanted generators. Of the 13 patients in whom the first displacement occurred more than 2 months after implantation of the electrode, 7 had an implanted and 6 an external generator at the time the incident occurred.

Threshold rise — Replacement of the electrode because of a rise i threshold was performed in 19 patients 22 times 12 were men and 7 women. In one patient 2 exchanges were made and in another 3 On one occasion the exchange was carried out within 2 weeks of the electrode being implanted. Nine replacements were made within a year and 9 more than 3 years after implantation — on average, 2 years (Table 10) The mean age of these patients, 63 5 (±2.7) years, did not differ appreciably from that for the whole series. Because of a rise in threshold in 2 cases the first generators implanted were replaced with ones worn externally and having a greater stimulating capacity but as their voltage was still too low for effective pacing, the wires were changed

In 11 electrode exchanges because of a rise in threshold the wire was so firmly attached to the endocardium of the right ventricle by a fibrous capsule that it could not be withdrawn. In 2 of these 11 patients the electrode tips were of platinum while the others were of stainless steel one new wire was inserted without clinical signs of tricuspid insufficiency

Until May 1964, the electrode tip employed was of stainless steel this kind of tip was used in 10 of the 19 patients in whom a replacement was made

Apart from the 19 whose electrodes were exchanged because of a threshold rise, in 6 an implanted generator was replaced by an external one to bring the stimulation power above an ncreased threshold. Of these 25 3 had angina pectoris, 3 severe arteriosclerotic lesions disclosed by coronary angiography and one a myocardial infarction confirmed by histologic examination. In one of the other 3 persons dying in this group autopsy disclosed diffuse general fibrosis, in another focal myomalacia of the myocardium and in the third myocardial metastases from carcinoma of the small intestine. In one of the patients who had angina pectoris and who used platinum electrod tip threshold values of between 5 and 8 V were measured in various parts of the right ventricle at the time the electrode was

changed. Of the 25 in whom there was a change of endocardial electrode or replacement of the subcutaneously implanted generator by an external one 20 had either a stainless steel electrode tip signs of CHD or verified changes of the heart muscle

Infection — Exchange of the endocardial electrode owing to surrounding infection was performed in 10 patients, in none of them more than once. Eight were men and 2 women the mean age was 61 years At the time of the infection that prompted the change of wire all 10 had an external generator In 2 this form of generator had previously replaced an implanted one because of infection in the pacemaker pocket. None of these patients had overt diabetes. In only one was septicaemia verified.

Septicaemia was found in 4 other patients, all with external generators. In one of them the dislodged endocardial electrode was not re implanted because of general infection and local infection in and around both jugular veins. The other 3 were given successful antibiotic treatment with the electrodes *in situ* One of the 4 had rheumatic mitral insufficiency the others showed no sign of rheumatic heart disease. One had 2 electrodes in the right side of the heart

Damage of the wire insulation — In 3 of the 5 patients where the transvenous electrode was known to be defective it was the insulation that was damaged, probably at the time the electrode was implanted or re positioned for the defect was always located on the part of the electrode between the supraclavicular fossa and its insertion in the jugular vein, the site of most surgical measures associated with implantation. In one of these cases the damage to the insulation was not found until autopsy and it was possibly responsible for the fatal outcome (p. 70)

In patients where an early prototype electrode having a stainless steel tip was used the defect was located between the wire and the tip

When, in a few patients, an attempt was made to withdraw the prototype electrode to exchange it, the tip came off Although these electrode tips found their way into a pulmonary artery where they remained for up to 4 years, they never caused the patient any trouble. In no case were there radiologic signs of pulmonary infarction.

EXCHANGE OF THE INDIFFERENT ELECTRODE

Data on the exchange of the indifferent electrode without simultaneous exchange of the transvenous electrode were available for 5 per cent of the patients (12/260) In one case the indifferent electrode was changed twice. Of these replacements 4 were performed within 12 months of implantation, in 2 cases owing to perforation of the skin and in the other 2 because of infection. In 3 cases the replacement was made because of annoying twitching of the skeletal muscles in the abdominal wall and in 3 others because of confirmed or suspected rupture of the wire. In 2 patients the electrode was changed — in one of them twice — because of an inadequate position. On several occasions the indifferent electrode was changed for one of more convenient length in connection with replacement of the generator These replacements are not reported here as they were not always annotated in the records

CHANGE OF IMPULSE GENERATORS

A fixed-rate impulse generator was implanted subcutaneously in the abdominal wall in 53 per cent of the patients (140/260) Up to the end of the observation

time such generators had been used for a total of 478 3 years.

The generators were implanted subcutaneously at different times after implantation of the electrode wire — on average 7 months (Table 11)

When the generator had been removed because of infection in the pacemaker pocket or a temporary rise in threshold and the external one had been worn for a time, 9 patients were furnished with a new subcutaneously implanted generator In 2 two re-implantations were performed after infection Fixed-rate generators were subcutaneously implanted in 140 patients. Of these, 68 (48 per cent) still had their first one at the end of the observation period on 31st March, 1968

In 52 per cent (72/140) of the patients with implanted fixed rate generators these were consequently exchanged before the end of the observation period. The change to this type was made in 59 per cent of the patients (43/72) to the triggered type in 21 per cent (14/72) and to the external type in 20 per cent (15/72) The exchange of the implanted fixed rate generator was performed once in 47 patients, twice 15 three times

TABLE 11 Time elapsing from i ertion of elec trod until implantation of the first fixed-rat impulse generator 140 patient

	Period (months)				
	<½	½—2	3—12	13—24	>24
No. of patients	40	37	41	13	9
Per cent	29	26	29	9	7

in 5 four times in 4 and fives times in 2 patients. There were altogether 118 exchanges.

The reasons for exchanging the fixed rate implanted impulse generator are shown in table 12. This includes the 5 patients in whom a faulty generator was found after autopsy Of the 9 patients responsible for the 12 replacements performed because of infection, 4 were given external generators. In 8 cases a change to an external generator was made because of infection in the pacemaker pocket or around the wire subcutaneously in the abdominal wall. Only 3 of the 19 patients where a change was made because of infection in the generator pocket, and/or skin perforation, had been paced for less than 3 years.

TABLE 12. Reason for ex hanging the implanted pacemaker g nerator (EM 137 139 141) and interval bet een implantation and exchange 118 ation

	Exchanges No	Per cent	Mean time (months)	S E
Routine	23	19	18 5	0 4
Proved or suspected malfunction	49	41	12 3	0.2
Infection in generator pouch	12	10	7.8	1.9
Perforation of the skin	3	3	9 0	4 6
Change to external because of				
threshold rise	9	8	10.6	5 3
infection	8	7	7 4	1 9
Other reasons	14	12	8.3	1.5
Total	118	100	11.7	1.3

In 9 patients with a stimulation threshold exceeding the voltage of the implanted generator a change to an external generator with a higher voltage was made. Six of them were subsequently furnished with another subcutaneous generator in 4 of these the endocardial electrode had previously been changed

The implanted generator was changed routinely after an average period of 17 months — in 22 cases after at least 16 months and in 9 after more than 18 months. The exchange of an implanted fixed rate generator as a safety measure or because of a suspected or confirmed defect was made after a mean of 12 months in 15 cases it had been in use for at least 16 months

In 8 patients the generator was implanted at the same time as the electrode wire This was done because they were suffering from cerebral confusion after frequent or protracted attacks of arrhythmic syncope, and a number of the first patients in that state pulled at the electrode wire and dislodged it.

GENERATOR FAILURE

Out of 205 fixed rate external generators (EM 138) changed and recorded at the Serafimer Hospital in the period 1962—67 and sent to the manufacturer for checking there was clinical suspicion of defect in 16 per cent (32/205) — in 16 cases based on fainting during pacing, and in 13 on an ECG-verified change in the generator rate, an oscilloscope-verified fall in voltage or a change in the impulse-wave form at the check. The check by the manufacturer disclosed defects in 13 per cent (27/205) of all external generators examined in 3 where there had been no clinical evidence of defect. Clinical suspicion of failure was confirmed in 75 per cent (24/32)

Out of 51 external generators of the most recently manufactured series sent for a checking, defects were found in 4 per cent, against 13 per cent of all the external generators checked.

DISCUSSION

One of the chief advantages of the transvenous electrode over the epicardial electrode is the simplicity of the implantation procedure.

In the present material the complications associated with electrode implantation were few and the mortality low In a series of 100 patients Harris *et al*[92] reported 2 cases in which the heart was perforated during insertion of the stimulating electrode. Yuceoglu, Lunger & Dresdale[222] reported 4 deaths among 78 patients during the surgical procedure, all of them occurring before the endocardial electrode could be positioned in the ventricle In a series comprising 19 patients provided with such electrodes Chardak, Gage, Federico Schimert & Greatbatch[11] found an immediate postoperative mortality of nil. In the present series the mortality during the electrode implantation was low compared with the immediate operative mortality of about 7 per cent when thoracotomy had been used[201]

In the present series a unipolar endocardial electrode was used that could be made extremely flexible in no case did this perforate the myocardium. This serious complication seems to be by no means rare[11, 48, 60, 69, 71, 92, 151, 161, 171] The lower risk of perforation greatly outweighs the disadvantage of the sometimes time-consuming procedure of getting the electrode into the right position in the apical region of the right ventricle

In no case was there clinically significant thrombosis around the electrode, but this

complication was found at autopsy in 2 cases[121] In a series by Zoll, Frank & Linen thal[220] clots around the electrode were also observed at 2 autopsies.

Complications associated with the transvenous electrode that called for corrective surgical measures or that were found at autopsy were recorded in nearly a third of the patients in this material during a mean follow-up time of 26 months. In one half of them the electrode was dislodged. Some authors[27, 78, illegible, illegible] have found late dislodgement a rare occurrence in the present series, too it usually happened within a few months of implanting the electrode, but in 10 more than 6 months elapsed.

Electrode displacement was more common in men than women, and in the patients under than over 50 years of age. These sex and age differences are not correlated, the relationship between men and women being largely the same for those under 50 years (15/11) as for the whole material (166/94) The higher frequency of this complication in the younger men is probably due to their greater physical activity

Pronounced enlargement of the heart has been considered to diminish the chance of getting an electrode wire to remain in place in the right ventricle[131, 201] In the present series the heart size was unrelated to the frequency of dislodgement. Harris and coworkers[illegible] suspected that there was a correlation between the use of an external generator and dislodgement. In the present series, too, a large proportion of patients where this complication was recorded were wearing an external generator there is, however no statistical correlation.

Formation of a fibrous capsule around the electrode[121] fixes it in the right atrium and ventricle and the eins and thus reduces the risk of dislodgement. The reason for the relatively common displacement in the patients of the present material with an external generator may be that it occurred before the formation of connective tissue around the wire. During this early period most of the patients had external generators. Among the few in whom there was dislodgement of the electrode more than 2 months after implantation the ratio of external to subcutaneously implanted was not different from that for the whole series

The need for re implantation because of dislodgement was less common in the series of Harris and co-workers[illegible] who implanted a loop of the endocardial electrode wire subcutaneously under the sternocleidomastoid and scalenus muscles. Even with this technique, however which was introduced in the present series in 1964[illegible] the number of dislodgements was quite high. In this series, as in others[illegible] it is evident that too much or too little wire inserted into the right side of the heart predisposes to dislodgement. The frequency of displacement in this series differed according to the surgeon[187]

Displacement does not occur f the wire is properly located in the apical part of the right ventricle and it describes a curved course in the right side of the heart. By having the patients walk from the operating theatre to the ward after implantation the positional stability of the electrode can be tested [167] Schwedel & Escher[illegible] have indicated the importance of the positional stability of the tip during respiration and coughing and in the erect, supine and lateral positions before finally securing the wire.

In a comprehensive examination of the method for estimating the stimulation threshold Siddons & Sowton[illegible] found that the threshold was dependent on the electrode material the impulse-wave configuration, and the duration of pacing. It is well

established that within a couple of months of beginning the pacing there is an initial rise, a fall and usually stabilization at a suitable level[43, 51, 98, 179] A late elevation of the threshold found in some patients of the present series has been observed earlier in connection with the use of both transvenous and epicardial electrodes[82, 83, 111] but in one pacemaker material with the latter type of electrode the threshold remained low and stable for as long as 4 years after installation[41]

The encapsulation by connective tissue is more pronounced with an electrode tip of stainless steel than with one of platinum[121] The denser the fibrosis around the tip the more powerful is the required stimulus[41, 51] Since May 1964, only platinum tips have been used

It has been stated that to obtain a lasting stimulation threshold during long-term pacing it is important for the area of the electrode tip not to exceed 50 mm^2 a larger area tending to increase the threshold[81] The tip of the stimulating electrode was reduced in size in January 1968.

On implantation an attempt should be made to obtain an electrode position for which the stimulation threshold is as low as possible, thereby reducing the likelihood of a threshold increase above the voltage of the generators. It is reasonable to suppose that CHD and other diseases resulting in changes in the myocardium increase the stimulation threshold. In the present series some of the patients with threshold elevations also had confirmed CHD and dispersed fibrosis of or metastasis in, the myocardium at autopsy

It has been found that the rise in threshold may be favourably moderated by steroids[178] In the present series these drugs were used in only a few cases for this purpose A more systematic use of steroids would possibly have reduced the number of cases in which a change in electrode was necessary

Infections around the endocardial electrode can produce sepsis[93, 148, 181, 183, 222, 225] sometimes leading to death[83, 111] In some cases of the present series the electrode was changed because of infection but in none of them was there confirmed septicaemia. In 4 other cases, however there was infection around the electrodes. In all but one of these cases the infection was cleared up by prolonged treatment with antibiotics with the electrode *in situ* This experience is inconsistent with the view that removal of the electrode is necessary if the infection is to be eliminated[83] All the patients in the present material with septicaemia or with infection that necessitated exchanging the stimulation electrode were using an external generator the portal of entry for the infection was always the site at which the wires passed through the skin. A higher frequency of infection around the stimulating electrode has been found among patients with an external than an implanted generator[83, 183] Even though the former type may be used for years without ensuing complications, the risk of perhaps serious infection is a factor that cannot be disregarded

A few electrodes with faulty insulation were found in the present series. Similar defects have been reported to a varying extent in respect of both epicardial[41, 211, 225] and endocardial electrodes[83, 148, 203] but there would seem to be a gradual improvement in this respect.

About one third of the present series were using an external generator in March, 1968, and 15 of them had done so for more than 4 years, a period considerably longer than has been reported hitherto for the external

generator. As stated above, the frequency of infection around the wire was higher for those with this type than for those with the implanted generator. In a few cases the external part of an electrode was accidentally cut while bandaging an infection at the site where it penetrated the skin. A few patients dropped their impulse generators, thereby dislodging the electrode. Despite the disadvantages associated with an external generator, of which the patients were informed, many that had been using this type for a long time were unwilling to change to an implanted one (p. 88).

As has been shown by Sowton in 1968[183], the rather high figure for established generator failures in the present study, as in an earlier report where the same type of impulse generator was used[21], is not unique. In a retrospective analysis of the number of failures in 341 completely implanted pacemaker units from 4 manufacturers (Devices, Ltd., Elema Schönander AB, Pye, Ltd. and Medtronic Inc.) Sowton found some kind of defect in 60 per cent of them; in 57 per cent it was generator failure. He concluded that the various types are equally satisfactory during the first year of pacing.

Some subcutaneously implanted impulse generators in this series were exchanged on grounds of their suspected failure. The need for such replacements can be significantly reduced by carrying out an oscilloscopic analysis of the performance of the implanted generators[43, 183, 185].

Pacing was discontinued in 12 patients of the whole series. The findings at the follow up examination for these patients will be outlined

Material — Of the 12 patients for whom the pacing was terminated 7 were men and 5 women their mean age at the start of pacing was 67 3 (±3 6) years (Table 13) The difference between this figure and that for the whole series is not statistically significant. The period of pacing up till termination of pacing ranged from one week to 8 months, mean 2.8 (±1 0) months. In all cases the pacing was introduced because of arrhythmic syncope in one heart failure was a contributory reason. Ventricular ectopic beats were registered in 10 of the 12 patients in this group before the treatment was started

Reason fo terminating pacing — In 8 of the 12 patients the reason for terminating *pacing was restoration of atrioventricular* conduction. Dislodgement of the endocardial electrode or a rise in the stimulation threshold was a contributory reason in 4 and the sole reason in 2 others. In one of them the electrode was dislodged after 2 months treatment it was implanted on the opposite side of the neck but displacement recurred. As the patient also has septicaemia the pacing was stopped One patient, a woman, developed cerebral confusion, probably as a result of cerebral bleeding from anticoagulant therapy which at that time was a routine treatment after insertion of transvenous electrodes at the Department of Thoracic Surgery Karolinska Hospital f nally the electrode tip came away from the wire and the pacing was terminated In another patient with an external generator the treatment was stopped after he had pulled out the transvenous electrode while in a state of alcoholic intoxication.

Rhythm at the term nation — At the time the pacing was terminated 6 patients had regular sinus rhythm, one had sinus rhythm and VEB 2 had variations between sinus rhythm and A V block II one of them with a prolonged P-Q interval, and 3 had complete heart block, one of them with VEB

Outcome and arrhythmic syncope after termination — Five of the 12 patients died after periods ranging from 1 week to 57 months, mean 14 months, after termination of the pacing. Before they died, 2 of them had attacks of fainting suspected of being due to arrhythmia. The mortality rate was not significantly higher than for the rest *of the series Out of the 5 deceased 3 had* died suddenly and one had arrhythmic syncope followed by lethal hypotension.

When one patient died suddenly during acute cholecystitis, he had lived for nearly 5 years after termination of pacing with CHB and no arrhythmic syncope. None of the 5 deceased had recent myocardial infarction at autopsy

At the postmortem examination of one of them there was recent, complete thrombotic occlusion of the internal jugular vein.

The 7 patients living at the end of the follow-up period were re-examined at least 4 months — mean 25 months — after pacing had been stopped. Four of them had

TABLE 13 Termination of treatment. Data relating to patients in whom pacing was stopped before the end of the observation period: 12 patients

No.	Patient: Age pacemaker inserted	Sex	Duration of pacing	Cause of termination	Rhythm at termination	Termination till follow-up or death, months	Attacks after pacing	Patient at follow-up
6	81	♀	4 mo	bleeding + cerebral confusion (+ electrode rupture)	CHB	71	?	alive
14	69	♂	12 d	dislodgement	A V blocks I and II	2	several	deceased
21	79	♂	2 mo	dislodgement + infection along the transvenous electrode	CHB	59	0	deceased
24	85	♀	7 mo	threshold elevation	CHB	9	0	deceased
62	51	♂	14 d	restoration of A V conduction	sinus rhythm	45	several	alive
101	47	♂	22 d			55	0	alive
116	58	♀	6 mo	threshold elevation		6	1	deceased
202	83	♂	2 mo	dislodgement + restoration of A V conduction	sinus rhythm and A V block II	18	2	alive
234	67	♂	2 mo	dislodgement + restoration of A V conduction	sinus rhythm	14	1	alive
238	60	♂	8 mo	restoration of A V conduction	sinus rhythm + VEB	14	0	alive
247	62	♀	7 d		sinus rhythm	13	1	alive
255	65	♀	10 d			1	0	deceased

had attacks of arrhythmic syncope and one was unable to answer this question at the re-examination.

DISCUSSION

Five of the 12 patients for whom pacing was discontinued died. Only 2 of the living had been free from arrhythmic syncope at the re-examination. Restored atrioventricular conduction, often combined with trouble with the transvenous electrode, was the most common reason for terminating the pacing.

If any conclusion may be drawn on the basis of the findings in this small number of patients it is that it seems unwise to stop pacing in patients that have had arrhythmic syncope, even if the atrioventricular conduction has been restored.

This section presents some anamnestic and objective findings in 260 patients receiving pacemakers at the Department of Thoracic Surgery, Karolinska Hospital, between February 196 and March, 1967 who were followed up until March, 1968. The method applied at the follow-up examination is reported in Section IV.

DEFINITIONS

Arrhythmic syncope (A.S.) Unconsciousness associated with ( ) ECG-recorded ventricular asystole, or PVTA during fainting, (*ii*) A V block II or CHB between fainting attacks, where no other explanation of loss of consciousness can be *offered*, and (*iii*) during pacing, likewise where there is no other explanation of the loss of consciousness.

Heart failure, severe. Diagnosis based on the existence of radiologically visualized pulmonary congestion, basal pulmonal rales, dyspnoea relieved by *sitting up* or *standing*, dyspnoea when walking on the level, hepatic distension and dependent oedema. This last sign was taken as the sole one only in cases in which some other sign had been recorded on an earlier occasion[183].

Heart failure, moderate. Reduction in physical capacity unaccompanied by the signs or symptoms mentioned under *Severe heart failure* above[183].

RESULTS

CLINICAL OBSERVATIONS PRIOR TO PACING

A slow pulse at (<50 beats/min) before pacing was observed or recorded in 92 per cent (240/260) of the patients in the series. The period elapsing from the time that the slow pulse rate was first noted or recorded until pacing was begun is given in table 14. In 12 per cent at least 5 years had passed (29/240); the mean was 19.4 (±2.0) months.

Time from first arrhythmic syncope until pacing. — Fainting due to arrhythmia before pacing was recorded in 90 per cent of the series (235/260) (Table 15). The time from the first arrhythmic syncope until introduction of pacing was on average 21.8 (±1.8) months; in 11 per cent (25/235) the interval was at least 5 years.

Frequency of arrhythmic syncope before pacing. — The mean number of attacks of arrhythmic syncope prior to pacing was 17 (±1.4) (Table 16). Twenty-five patients had had none and 7 more than one hundred.

Clinical picture associated with arrhythmic syncope. — The clinical picture during the attacks is summarized in table 17. Of the 25 patients that had had no attacks before pacing was begun 18 reported dizziness. For one half of the series the attacks of arrhythmic syncope were unaccompanied by any other symptoms. Cerebral confusion following several attacks or such of long duration occurred in 8 per cent (20/260) of the patients at the time pacing was begun; only 4 of these were under 70 years of age; the mean was 75.3 (±2.9) years, against 65.7 (±0.8) for the whole material; this difference is statistically significant ($P<0.01$).

Injury associated with arrhythmic syncope was recorded in 25 per cent (52/207) of the patients for whom information was available. It consisted of fractured skull in

TABLE 14 Interval between first observation of slow pulse or heart rate and start of pacing 240 patients

Time Interval (months)	<½	½—1	2—6	7—12	13—36	37—60	>60	Total
No. of patients	67	31	42	29	23	19	29	240
Percentage	*28*	*13*	*17*	*12*	*10*	*8*	*12*	*100*

TABLE 15 Interval between first arrhythmic syncope and start of pacing 233 patients

Time Interval (months)	<½	½—1	2—6	7—12	13—36	37—60	>60	Total
No of patients	42	27	36	30	47	28	25	233
Percentage	*18*	*11*	*15*	*13*	*20*	*12*	*11*	*100*

TABLE 16. Number of attacks of arrhythmic syncope before pacing

No. of attacks	0	1	2—4	5—10	11—30	31—100	>100	Total
No of patients	25	14	40	72	73	29	7	260
Percentage	*10*	*5*	*15*	*28*	*28*	*11*	*3*	*100*

3 cases, in 2 of whom there was intracranial haemorrhage, and external cranial injuries calling for stiches in 45 Fractures of the extremities were encountered in 4 cases

Resuscitation — Resuscitation had been performed in 19 per cent (48/260) of the patients — usually as external heart massage Defibrillation in PVTA and thumping over the precordium in asystole had also been performed Several patients had fractures of the ribs after the resuscitatory measures

Epilepsy and EEG — Epilepsy was diagnosed in 12 per cent of the series (27/233) and one half of these had received antiepileptic drugs before arrhythmic syncope was diagnosed. In 2 there were focal neurologic symptoms during arrhythmic syncope, which changed to general convulsions. Six patients in whom epilepsy was diagnosed before implantation had attacks of arrhythmic syncope during pacing in 3 of them no defect in the pacemaker system could be found, but the attacks of unconsciousness were not of the epileptogenic type with aura and focal convulsions, and none of them was accompanied by epileptogenic EEG activity Of the 26 per cent of the patients (68/260) in whom EEGs were registered, 5 displayed focal activity 34 nonspecific changes, and 29 normal EEGs. None of the patients with focal activity before implantation fainted during pacing.

Dizziness — In 10 per cent of the patients (25/233) there was dizziness that was judged *not* to be due to arrhythmia of these, 2 had Menière's disease and one otogenic vertigo induced by streptomycin In the other patients the dizziness was classed as non-specific, and was probably caused by arteriosclerosis.

Indications for pacing — In the majority of the cases the main indication for pacing was attacks of arrhythmic syncope (Table 18) Next in order were severe and moderately severe heart failure In 8 patients the indications were uncommon CHB with slow

haert rate and shock were the indications in 2 patients, and invalidating dizziness ascribed to arrhythmia in 2, one of them also having cerebral confusion. One patient with CHB and no symptoms was paced because of this conduction defect. One patient with A V block II and ventricular ectopic beats but no symptoms was paced to prevent PVTA CHB moderate heart failure and principally a secondary mental depression were indications in one case. In one patient with a renal tumour and complete heart block, pacing was introduced to prevent serious arrhythmia in connection with planned aortography and any subsequent operation.

TABLE 17 *Sign and symptom ascribed to arrhythmia before pacing*

	No of patients	Per cent
No symptoms	7	3
Dizziness	18	7
Syncope	127	49
Syncope and muscular spasms or convulsions	57	22
Syncope and spontaneous incontinence of urine and/or faeces	36	13
Syncope and cerebral confusion after attack( )	15	6
Total	260	100

TABLE 18 *Indication for pacing*

		No. of patients	Per cent
Arrhythmic syncope		200	77
Severe heart failure	+ A.S	25	9
	no A.S	6	2
Low physical capacity	+ A.S.	9	4
	no A.S.	14	5
Other indications		8	3
Total		260	100

CLINICAL FINDINGS DURING PACING

In 23 per cent (55/243) of the series for whom relevant information was available, *arrhythmic syncope* was recorded during pacing. Most of the patients only had one attack. 51 per cent (28/55) of these were ascribed to defects in the pacemaker unit (p 41) If the patients having no attacks before pacing are disregarded the frequency of arrhythmic syncope during stimulation was 25 per cent (54/219) Apart from the syncope, 19 per cent of the patients (32/243) also had dizziness that was judged to be due to arrhythmia One of them, who had never lost consciousness before introduction of pacing, had arrhythmic syncope subsequently

Of the 27 patients with arrhythmic syncope during pacing for whom no defect in the unit could be found 11 had VEB before pacing against 31 out of 188 that had no syncope during pacing. This difference is not statistically significant.

In none of the paced patients with arrhythmic syncope was there evidence or a history of fracture, external skull injury or concussion during the attacks of arrhythmic syncope

Cerebral confusion — In only one of the 20 patients with cerebral confusion at the time pacing was begun did this condition persist until death, 6 weeks later

Feeling of arrhythmia. — A sensation of arrhythmia was experienced by 44 per cent (97/223) during the pacing. Of these, 66 per cent (64/97) recorded competition and/or VEB against 40 per cent (50/126) of the other patients for whom data were available The difference is significant ($P<0.001$)

Muscular twitching around the indifferent electrode — Twitching of the abdominal muscles in the vicinity of the indifferent electrode was experienced in 42 per cent of the patients (75/177) In most cases this

was also annotated in the records or was observed at the follow-up examination. The twitching usually diminished during pacing, and in only one case was there recorded evidence that the position of the indifferent electrode was changed for this reason (p. 00)

Sedatives hypnotics and/or psychopharmacologic drugs — Such drugs were used regularly during pacing by 32 per cent of the patients (81/253) men and women were equally represented (41 and 40 respectively) These drugs were used more often by the patients that experienced a sensation of arrhythmia than by those that did not (41 and 26 per cent, respectively 37/91 and 24/92 $P<0.05$)

Heart failure — Signs or symptoms of severe heart failure were found at the follow-up examination in 34 per cent (68/181) of those surviving and still being paced at that time. Of these, 63 per cent (65/104) were men and 37 per cent (39/104) were women the mean age was 69 (±1 0) years. Only 2 of the 25 patients under 50 years and 9 of the 40 under 60 years at the time the pacemaker was provided displayed signs of severe heart failure.

Of the 29 patients for whom the heart failure contributed to, or was the main reason for pacing 9 had died by the end of the follow-up period 4 of them from heart failure. In one case the pacing had been terminated. Fourteen of the other 19 still had heart failure at the follow-up 12 were treated with digitalis and 13 with diuretics In only 2 of the 29 did the pacing result in an appreciable subjective and objective improvement in the heart condition.

Digitalis and/or diuretic treatment — Of those living and being paced at the follow up examination, digitalis therapy was being given regularly to 40 per cent (73/184) and diuretics to 40 per cent (72/182) while 26 per cent (48/182) were taking both types of drugs.

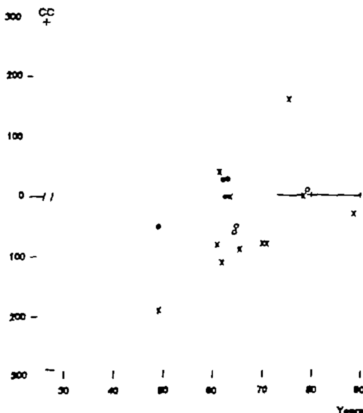
RADIOLOGIC EXAMINATION OF THE HEART

Near time of implantation — Reports on heart and lung radiography including a heart volume determination, were available for 96 per cent of the patients (250/260) In 82 per cent of these (206/250) the radiologic examination was performed within the 2 months preceding or following electrode implantation. The heart size at about the time pacing was begun was on average 1082 (±24 1) cc and 577 (±12.9) cc/m² for the men and 806 (±18.6) cc and 488 (±10 1) cc/m² for the women for the whole series the values were 983 (±18 7) cc and 545 (±9 5) cc/m²

For the 104 patients with severe heart failure during pacing the mean heart volume, where determined, at about the time of implantation was 625 (±17 0) cc/m² against 471 (±9.5) cc/m² for those where there was no evidence of heart failure the difference is statistically significant ($P<0.001$)

Comparison of the heart size before and during pacing — The patients for whom a radiologic examination was performed both within a month before and a month after implantation and for whom digitalis or diuretic treatment was *not* begun in the intervening interval numbered 54 (Fig 8) The mean relative heart volume for these patients before pacing was 597 (±22.7) cc/m² and after insertion of the electrodes 564 (±22 7) cc/m² the difference is not statistically significant. As is seen from figure 8, the change in heart volume during the relevant period is uncorrelated with age. Nor was there any difference in the change in heart volume between those dying during the observation period and the other patients.

Figur 8. Change in the relative heart volumes between radiographic examinations performed within one month before and after start of pacing versus patient age. Increase (+) in heart volumes above the horizontal axis, decreases (—) below. ... denotes alive and ... dead at end of observation period. 54 patients.



DISCUSSION

As, according to the classical descriptions by Morgagni[190], Stokes[190] and Adams[190], Stokes-Adams attacks occur only in patients with a slow heart rate and attacks of unconsciousness, the term arrhythmic syncope has been used in this report. It is thus possible to include in this concept patients with CHB or A V block II but without bradycardia, patients with other arrhythmias where the heart rate is normal between the attacks, and patients with tachycardia with attacks of PVTA or asystole.

A long period elapsed from the time a slow pulse was first noticed or a slow heart rate recorded, or from the first attack of arrhythmic syncope, until pacing was begun. It would thus seem that prior to pacing some of the patients were living many years with an intermittent or constant conduction defect. That patients with CHB can survive for several years without a pacemaker is well documented[35, 60, 77, 86, 175, 181].

At the time the pacemaker was implanted several of the older patients were suffering from confusion after frequent or protracted arrhythmic syncope. In all but one of them the condition disappeared — usually, however, only after a day or so of stimulation, occasionally after several days. In this category of patients Schwedel & Escher[181] also found a marked clearing of cerebral symptoms after a short period of pacing. Cerebral confusion following frequent or protracted arrhythmic syncope should thus not be regarded as contraindication for pacing.

Some of the patients with cerebral confusion who wore external generators during the early stage of the treatment involuntarily pulled on the electrode wires and in some cases dislodged the endocardial wire After this early pacemaker experience it therefore became the practice in the case of cerebrally confused patients to implant the generator subcutaneously at the same time as the electrode (p 42)

Arrhythmic syncope during pacing was recorded in nearly one quarter of the patients compared to 90 per cent before the pacing In one half of them some form of pacemaker failure was established. The others might possibly have had PVTA that the stimulation did not suppress they would then have had a higher frequency of ventricular ectopic beats than those not fainting during the pacing, since the former were correlated to that of PVTA (p 58) but this was not the case. Undisclosed defects in the pacemaker unit would also account for these attacks of unconsciousness.

Injury in connection with arrhythmic syncope was fairly common before, but not during pacing. This is probably due at least in part to the appreciable higher frequency of arrhythmic syncope before than during the pacing It is also possible that the sensation of arrhythmia more often preceded arrhythmic syncope during than before pacing, with the result that the patients could take the requisite measures.

A diagnosis of epilepsy was not uncommon before fainting was recognized as arrhythmic syncope and pacing was introduced. It cannot be ruled out that, in patients with complete heart block and restricted cardiac output before pacing, an ischaemic epileptogenic focus was eliminated on raising the heart rate by pacing. Sulg[200] has reported a tendency for normalization of the frequency histogram of the EEG curves after an increase of the heart rate in pacemaker patients. The clinical picture during the arrhythmia induced fainting attacks that has been described by Landegren & Biörck[131] was, however found in most of the cases in this material arrhythmic syncope characterized by a sudden and unexpected onset, pronounced pallor followed by flushing upon recovery of consciousness, which is usually complete within a few seconds. The possibility that the improved circulatory state resulting from the pacing suppressed the effect of an ischaemic cerebral focus is therefore small.

The term moderate heart failure is utilized to denote symptoms of heart failure that are undetected at rest and that accompany low ventricular rate *and* moderate physical activity A reduced physical capacity at low ventricular rates has been demonstrated in experimental studies[8, 11] Severe heart failure should probably not occur in moderate, but possibly in extreme, ventricular bradycardia that is unaccompanied by heart muscle lesion this is contradictory to the above criteria for moderate heart failure.

As data on the occurrence of heart failure prior to pacing were not available in all the patients it is impossible to draw any conclusions as to the effect of this measure on heart failure In some patients this condition was at least a subsidiary indication for pacing An appreciable improvement in the heart condition was found in only 2 of them a number died from heart failure in spite of the pacing, and in several the condition was still present at the follow up here, there was probably more or less general lesion of the heart muscle, together with damage to the atrioventricular system this was verified at autopsy in patients with severe heart failure (p 78) Heart failure combined with

CHB has been considered to be an indication for pacing[9, 31, 159, 181, 223] and support for this view is provided by experimental studies[6, 8, 18, 40, 50, 185] showing that an acceleration of the heart rate by pacing improves the circulation.

A limiting effect of pacing on gross congestive heart failure in CHB has been mentioned elsewhere[111, 201]. No significant reduction in the radiologically determined heart volume as a result of the pacing was found; however, by no means all the patients underwent this examination within a month before and after pacing was started — the intervals within which the comparisons were made.

IX. ELECTROCARDIOGRAPHIC FINDINGS BEFORE AND DURING PACING

The object of this part of the study was to analyze the ECGs recorded between and during the attacks of fainting elicited by ar rhythmia before and during pacing and also during short intervals when the pacing was interrupted In addition comparison was made of the A V conduction before and during pacing.

METHODS AND DEFINITIONS

The electrocardiograms at the follow up examination were obtained with a 4-channel direct writing ink jet recorder (Mingograph 42 Elema Schönander Stockholm) Leads I II III $CR_{1,2,4,6,7}$ aVR, aVL, aVF $V_{1,2,4,6}$ and $_7$ were used with a paper speed of 50 mm/s, and $CR_{2,4,6}$ and $_7$ at a speed of 25 mm/s This method was also used in obtaining most of the ECGs examined both before and during pacing. The ECGs for determining the time that conduction defects appeared were usually recorded with fewer leads.

In calculations of the atrial and ventricular rates at least 3 P P or R R intervals were used. The diagnostic criteria for right (RBBB) left (LBBB) and anterolateral bundle branch block (ALBBB) are those customarily used[5, 85]

A V block I — A P Q interval of at least 0.22 s in any of the leads I, II III, aVL or aVF

A V block II — One or more isolated blocks of P waves or systematic 2 1 3 1 blocking after non-premature P waves in the case of an atrial frequency of less than 180 beats/min.

Complete heart block (CHB) — Completely independent atrial and ventricular activity and essentially regular ventricular rhythm not exceeding 60 beats/min.

Asystole and sinus arrest — Sudden arrest of regular ventricular or atrial activity for more than 2 seconds.

Cardiac arrest — Simultaneous atrial and ventricular arrest.

Paroxysmal ventricular tachyarrhythmia (PVTA) The registration of at least 3 ventricular complexes of at least 0.12 s in close succession and in configurations differing from the other ventricular complexes. This term includes ventricular fibrillation.

Ventricular ectopic beats (VEB) — Premature ventricular complexes with a QRS width of at least 0 12 s within a rhythm of QRS complexes of less than 0 12 s VEB during pacing imply QRS complexes of at least 0 12 s, with a different configuration from any idioventricular complexes recorded before pacing or during any break in the pacing.

Competition — Supra- or idioventricularly elicited beats between 2 pacer-elicited complexes or one such complex and a pacemaker impulse in the refractory period

Asystole during breaks in pacing — Absence of established idioventricular rhythm in a patient using a variable rate external generator despite stimulation for some minutes at the lowest frequency

TABLE 19 Time elapsing from the first registratio of A-V block I and II and CHB until the pacing

		Minimum time elapsing until pacing (years)							
		1		2		3		5	
	No. of patients	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent
Conduction defect									
A-V block I	77	38	*50*	27	*36*	24	*32*	18	*24*
A-V block II	99	29	*29*	20	*20*	16	*16*	13	*13*
CHB	236	63	*27*	45	*19*	37	*16*	25	*11*

RESULTS

ECG BEFORE PACING

A-V block I II and CHB — A V block I was recorded in 77 A V block II in 99 and CHB in 236 patients at varying times before pacing.

On average A V block I was recorded 41 (±6.9) A V block II 13 (±2.3) and CHB 12 (±1.6) months before pacing CHB had been recorded for as long as 23 years before pacing was introduced. The time elapsing from the first registration of A V block I and II and CHB until the time of pacing is reported in table 19

In 68 patients both A V block I and CHB were observed, and on different occasions. For these patients the mean time elapsing between the first registration of an A V block I and start of pacing was 43 6 (±7.6) months. The corresponding time for CHB was 25 (±5.2) months the difference is not significant. A V block II or CHB was recorded before A V block I in 6 patients

Variations in heart rhythm — For 253 patients at least 2 ECGs had been registered before pacing (Table 20)

Heart rhythm in the patients without CHB — Complete heart block was not recorded in 24 patients. Of these, 10 had A V block II, 10 had sinus bradycardia and 2 had sinus rhythm with a normal rate and numerous VEB, one of them with registered PVTA. Two patients had atrial fibrillation with a varying ventricular rate and numerous VEB one of them had PVTA. Of the 10 patients with A V block II but no ECG registration of CHB, sinus rhythm or A V block I was registered after the A V block II in 8 cases All these had attacks of arrhythmic syncope before pacing and in 3 of them asystole was recorded All but one had a bundle branch block configuration of the ventricular complexes.

Arrhythmic syncope before pacing was found n all but one of the patients in whom

TABLE 20 Variation in heart rhythm before pacing, 253 patients with at least 2 ECG registrations

	No. of patients	Per cent
Heart rhythm		
Sinus rhythm with BBB and/or P-Q interval >0 22	12	*5*
Atrial fibrillation with varying rate	2	*1*
A-V block II	1	
Variations between sinus rhythm with BBB and/or P-Q interval ≥0 22 and A V block II	9	*4*
CHB	82	*32*
Variations between A V conducted rhythm and CHB	147	*58*
Total	253	*100*

TABLE 21 Heart rhythm at the last ECG registration before pacing

	No. of patients	Per cent
Heart rhythm		
Sinus bradycardia	9	3
Sinus rhythm	16	6
+VEB	5	2
A V block II	23	9
+VEB	8	3
CHB	157	61
CHB+VEB	42	16
Total	260	100

only sinus rhythm was recorded thus patient had sinus bradycardia with a minimum rate of 32 beats/min. Five of the 10 with sinus bradycardia registered sinus arrest.

Atrial fibrillation or flutter was recorded in 39 (16 per cent) of the 256 patients for whom an atrial rhythm was registered prior to pacing In 30 these arrhythmias occurred in all registrations before pacing and in 9 intermittently

Ventricular ectopic beats were recorded on some occasion prior to pacing in 43 per cent (112/260) In all but 3 of the 38 with ECG-verified PVTA there were VEB at rest, compared with 29 out of 84 (35 per cent) with only ECG-registered asystole the difference is significant ($P<0.001$)

Coronary heart disease (p 22) was diagnosed in 68 patients of the series 38 of these (55 per cent) had VEB a frequency that is higher than for the patients without diagnosed coronary heart disease ($P<0.05$)

ECG observations during arrhythmic syncope — Of the 235 patients that had arrhythmic syncope before the pacing, ECGs were registered during fainting in 52 per cent. The ECG showed asystole in 84 (69 per cent) PVTA in 27 (22 per cent) and both asystole and PVTA in 11 (9 per cent) of them. On 3 occasions asystole and PVTA were recorded on the same ECG Cardiac arrest was recorded in 7 patients of the whole series. Asystole was registered in a patient who had dizziness without arrhythmic syncope

The mean duration of the circulatory arrest, recorded in the ECG of 57 patients, was 35 s (range 2—140) Durations of at least 30 s were registered in 15 patients, 8 of them with PVTA and 7 with asystole By the end of the observation period 12 of these had died one after pacing had been discontinued

Circulatory arrest was recorded before pacing in 61 per cent (56/88) during the first 3 years (February 1962—February 1965) and in 45 per cent (66/147) during the last 2 years of the period over which the series was collected (March, 1965—March, 1967) the difference is statistically significant ($P<0.01$)

ECG observations in patients without arrhythmic syncope — Among the 25 patients furnished with a pacemaker without having had attacks of arrhythmic syncope there were 13 in whom only CHB had been registered before pacing, while 11 had shown variations between conducted rhythm and CHB, and one sinus bradycardia. In one of those without arrhythmic syncope short periods of asystole were registered

There were more patients without arrhythmic syncope among those with stable CHB (15 per cent 13/85) than among those with alternating supra and idioventricular rhythm (7 per cent 10/147) This difference is significant ($P<0.01$)

The rhythm preceding pacing — Conducted heart rhythm was recorded just before pacing in 23 per cent (Table 21)

Ventricular rates in A V block II and CHB — The lowest ventricular rate recorded for each patient before pacing was

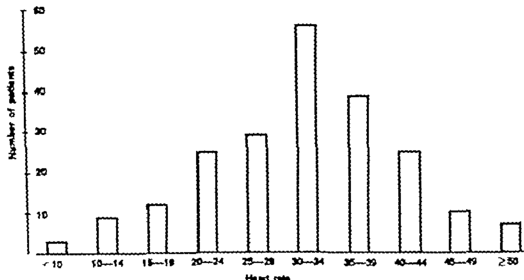


Figure 9 Heart rate in CHB 236 patients

on average 40 (±0.09) beats/min (range 20—86) in A V block II and 31 (±0.07) beats/min (range 6—60) in CHB. Of the 215 patients with CHB where the heart rate was measured, 3 patients had a value of less than 10 beats/min and 24 (11 per cent) less than 20 beats/min (Fig 9)

For the patients with certain diseases the means of the lowest recorded ventricular rates in CHB are presented (Table 22). There was no statistically significant difference in the means of these rates.

P-Q interval — A V block I was recorded in 77 out of the 260 patients in the series. The longest intra-subject P-Q interval for the 72 patients where this could be determined was on average 0.28 (±0.008) s. For the 50 men it was on average 0.30 (±0.010) s, and for the 22 women 0.24 (±0.006) s. The interval was significantly longer for the men than the women ($P<0.001$)

For the patients with uropolyarthritis, moreover, it usually increased gradually be

TABLE 22 Means of the lowest registered idioventricular rates for patients with certain conditions

	No of patients	Mean (beats/minute)	S E
Coronary heart disease	63	34.1	1.2
Diabetes	25	34.5	2.1
Myocarditis	10	22.5	3.5
Rheumatic valvular diseases	19	30.9	2.7
Uropolyarthritis	8	29.4	5.2
Total with CHB	236	31.3	0.6

TABLE 23 Various types of bundle branch block in 178 patients with conduction defect but atrio-ventricular conduction

	No. of patients	Per cent
BBB pattern		
RBBB	60	*34*
LBBB	47	*26*
Alternating RBBB and LBBB	8	*5*
RBBB+ALBBB	13	*7*
Atypical BBB	7	*4*
QRS <0 12 s	43	*24*
Total	178	*100*

TABLE 24 Heart rhythm (ECG) during pacing, 251 patients

	No. of patients	Per cent
Heart rhythm		
Constantly regular pacemaker induced rhythm	119	*48*
Competitive rhythm	96	*38*
Paced rhythm with VEB	36	*14*
Total	251	*100*

fore the conduction defect changed to a higher grade of block. The P-Q interval for men without uropolyarthritis was 0.28 (±0 018) s. The difference in between these men and women is still significant ($P<0\ 001$)

Bundle branch block — Eleven per cent (20/178) of the patients had had bundle branch block for more than 2 years before A V block I or II or CHB was recorded In one patient the bundle branch block had been registered 18 years before any other conduction defect.

The distribution of the various types of bundle branch block concomitant with other conduction defects than CHB and the number of A V block I or II without bundle branch block are presented in table 23

QRS width less than 0 12 s in CHB — In altogether 23 per cent (54/236) of the patients the QRS width in CHB was normal. Fourteen patients of the series had suspected congenital CHB 5 of these had a QRS width of less than 0 12 s. Of 25 patients without arrhythmic syncope 6 recorded a QRS width of less than 0 12 s simultaneously with CHB Of those without arrhythmic syncope before pacing the number with a QRS width of less than 0 12 s and CHB was not statistically different from that for a QRS width of at least 0 12 s and CHB

ECG DURING PACING

The ECGs recorded during stimulation with a fixed rate impulse generator are presented in table 24. About one half of the patients showed regular paced rhythms.

During pacing atrial fibrillation or flutter was recorded in one or more ECGs in 24 of the 30 patients that, prior to pacing, had had atrial arrhythmia at *all* registrations. Of the 9 patients with intermittent atrial fibrillation or flutter before pacing only one showed the same type of arrhythmia during pacing. During pacing VEB were recorded in 24 per cent (27/111) of those with VEB and 6 per cent (8/147) of those without VEB before pacing the difference is significant ($P<0.001$)

ECG REGISTRATION WITH PACEMAKER DISCONNECTED

In connection with the check of externally generators ECGs were registered during a short break in the stimulation in 72 per cent (186/260) of the patients. This was usually performed within 3 months of the patient receiving electrodes and before

subcutaneous implantation of generators. The results are shown in table 25. In about one half the patients CHB was recorded consistently. No ventricular activity was recorded in 13 of the patients during an effort to switch off the generator. With the pacemaker switched off VEB were recorded in 28 per cent (24/85) of the patients that had VEB before pacing and in 6 per cent (6/101) of those that had not. The difference is statistically significant ($P<0.001$).

TABLE 25. Heart rhythm registered during brief interruption in pacing, 186 patients

	No. of patients	Per cent
Heart rhythm		
Sinus rhythm with BBB and/or P-Q interval > 0.22	40	*22*
A-V block II	6	*3*
CHB	91	*49*
Variations between conducted and idioventricular rhythm	36	*19*
Asystol	13	*7*
Total	186	*100*

COMPARISON OF ECGs BEFORE AND DURING PACING

Out of 157 patients with ECG-recorded complete heart block just before implantation of the electrodes, 85 (54 per cent) had only a regular paced rhythm and no VEB when the fixed-rate pacemaker was in use, and 48 (46 per cent) had only CHB and no VEB when the generator was switched off. Moreover, 10 per cent (11/105) had ventricular asystoles during attempts to discontinue the electrical stimulation. In the 61 patients with conducted heart rhythm just before implantation 7 had CHB without VEB when the pacemaker was switched off.

Out of 82 patients with CHB on all occasions of registration before pacing 56 per cent (46/82) had only regular paced rhythm and 49 per cent (28/57) only CHB during interruption of pacing at the checks.

During interruption 82 of the 186 for whom the pacemaker could be switched off at checks had A-V conduction (45 per cent). Of the ECGs registered just before pacing was started among them, 44 (24 per cent) showed conducted ventricular activity. This higher frequency of conducted rhythm during than before the pacing in the patients where the pacemaker could be switched off is significant ($P<0.001$).

Of the 46 in whom only conducted heart rhythm was recorded with the pacemaker switched off 8 (17 per cent) had only CHB but in none of them had this been recorded for more than a month *before* the pacing was begun. Of the 82 patients recording conducted rhythm on some occasion with the pacemaker switched off 16 (19 per cent) had only CHB before the pacing, 2 of them for more than one month.

DISCUSSION

The arrhythmias and other ECG changes reported here, most of which were recorded during short registrations, were not, in all probability the only ones present before and during the pacemaker stimulation. The number of registrations and the time elapsing between the first and the last, both before and during pacing, varied greatly from one patient to another. In spite of these shortcomings certain differences are evident that have made it possible not only to characterize the registered heart rhythms but also to examine their implications from certain clinical aspects.

In a review of the ECGs recorded during

TABLE 23 Various types of bundle branch block in 178 patients with conduction defects but atrioventricular conduction

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During pacing atrial fibrillation or flutter was recorded in one or more ECGs in 24 of the 30 patients that, prior to pacing, had had atrial arrhythmia at *all* registrations. Of the 9 patients with intermittent atrial fibrillation or flutter before pacing only one showed the same type of arrhythmia during pacing. During pacing VEB were recorded in 24 per cent (27/111) of those with VEB and 6 per cent (8/147) of those without VEB before pacing: the difference is significant ($P<0.001$)

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In connection with the check of externally generators ECGs were registered during a short break in the stimulation in 72 per cent (186/260) of the patients. This was usually performed within 3 months of the patient receiving electrodes and before

patients having conducted heart rhythm before CHB.

Ventricular ectopic beats were recorded some time prior to pacing in as many as 43 per cent of the patients and in no less than 92 per cent of those with recorded PVTA. Unless VEB have been registered the probability that PVTA is the arrhythmia causing syncope is extremely small.

Large variations in the ventricular rate in complete heart block have been reported[99]. The mean rate for 6 CHB series ranged from 35 to 43 beats/min[31, 36, 99, 103, 176]. Extremely slow ventricular rates seem to be rare in CHB[169]. In the present series, however, 11 per cent of the patients with CHB registered before pacing had a ventricular rate of less than 20 beats/min. As slow rates are more significant than the average rate as an indication for pacing[132], the mean was calculated only for the lowest rate for each patient in the series. A mean rate of 31 beats/min — that is, slower than in the above-mentioned materials — is thus hardly remarkable finding.

More patients in this series recorded atrioventricular conduction during a short interruption in stimulation (44 per cent) than just before pacing was begun (23 per cent). A high frequency of permanent or intermittent restoration of sinus rhythm in 68 paced patients followed for at least one month has been reported by Donato, Giuntini, Mariani, Cantine, Barsotti & L'Abotte[88]. Competition was common (51 per cent) also in the present series.

That pacing did not result in an appreciable change in the frequency of VEB is astonishing, as in a CHB series reported by Campbell[35] an abnormally slow heart rate was often associated with regular bigeminal VEB. This phenomenon was also observed in the present series when the stimulation rate was lowered on changing an external generator. The high frequency of occurrence of VEB registered at rest in the paced patients recording VEB also before pacing was begun, points to heart muscle lesion. Support for this view is found in the higher frequency of VEB in the patients with coronary heart disease and the deceased than among the other patients still alive at the end of the observation period.

The occasionally observed change in rhythm between the time just before pacing was introduced and the registration during pacing is one reason for using the two-stage procedure, the first stage consisting in insertion of the electrode wire and its connection to an externally worn generator and the second stage the implantation of the definitive type of generator. The common occurrence of competing idioventricular or supraventricular rhythm or VEB during stimulation points to a fairly great need for triggered generators or ones of the demand type in patients with the indications in the present series.

X. SURVIVAL TIME WITH PACEMAKERS

The survival for the decades in the series with at least 20 members was compared with that for the general population. Furthermore, the survival in the general population was compared with that for the whole series after 12 months of pacing. After the exclusion of the patients where the pacing was discontinued and those dying during the first year a new comparison was made 2—5 years later

RESULTS

Of the 248 patients furnished with transvenous electrodes between February 1962, and March, 1967 and for whom pacing was not terminated, 25 per cent (62 patients) had died by 31st March, 1968 The 5 dying after termination of pacing have been reported above (Section VII)

The one-year survival was 86 per cent (Table 26) this is significantly lower than a calculated mean survival for a group from the general population with the same age and sex distribution as in the present series (95 per cent) The cumulative survival is also shown in figure 10

The time during which the material was collected has been divided into 5 periods, the first of 14 months and the others of 12 months the survival was largely the same for the patients entering the series during any of the 5 periods.

The survivals after 2 and 3 years did not differ significantly from those for the general population estimated for the same periods, on the other hand, for the 4- and 5 year survivals the differences again became significant (Fig 11)

The mean survivals for the decades of women and the 4 of men having at least 20 patients and the same decades in the population were compared. The results are presented in figure 12. The mean survival for the population was calculated for the 5-year period from the middle of the decade

TABLE 26 Life table for all the material according to Cutler et al[48]

	Alive at beginning of interval	During interval			Cumulative survival (per cent)
		Died	Pacing terminated	Withdrawals	
Interval in relation to start of pacing					
0—12 months	260	35	12	0	86.2
13—24	213	11	—	85	80.6
25—36	117	9	—	47	72.9
37—48	61	7	—	19	63.0
49—60	35	—	—	16	63.0
61—	19	—	—	18	63.0
>72	1	—	—	1	

DISCUSSION

As the patients were summoned regularly for pacemaker checks and any case of absence was immediately looked into all the deaths were recorded If the reason for a patient's absence could not be found in any other way enquiries were made at the appropriate parish office[1]

The one-year survival for the present series was considerably higher than for the 406 CHB patients comprising 3 other series — 86 against 51 per cent[48 71 183] but the materials are not fully comparable, as the present series includes patients for whom total block was not recorded omission of these does not, however appreciably affect, the one year survival (85 per cent 191/224)

The one year survival for the present series does not d ffer significantly from the 83 per cent reported by Sowton for 344 patients comprising 7 pacemaker series[201] The 2-year survival of 81 per cent for the present series, including deaths at operation, does not differ significantly from that for the 30 patients followed up for the same time in pacemaker series presented by Chardak, Gage, Federico Schumert & Greatbatch[42] The survival during an observation period of up to 6 years was high

The 12 month survival for decades containing at least 20 patients was considerably lower than for persons of the same age and sex in the general population. This difference tended to diminish during the observation period.

In Sweden register of births, deaths marriages and other personal data is kept at the local parish offices

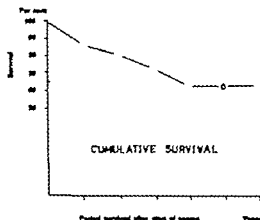


Figure 10 Period survived after start of pacing.

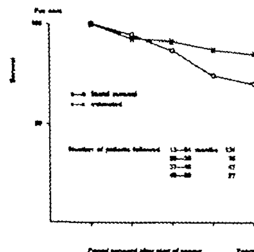
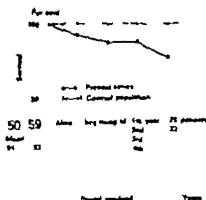
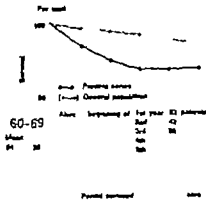
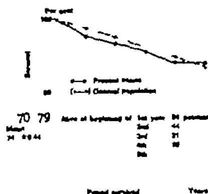


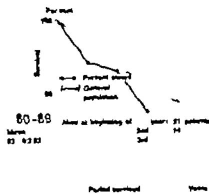
Figure 11 Survival rates after 2—5 years of pacing the patients dying or for whom the pacing was terminated during the first year has been excluded

MEN

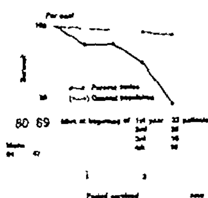








WOMEN



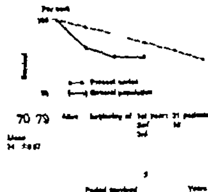


Figure 12 Period survived by patients in decades with more than 20 members and the corresponding decades in the general population

XI. MODE OF DEATH AND POST MORTEM FINDINGS

An analysis of the postmortem findings was made with the prime purpose of ascertaining the extent to which sudden death might be ascribed to the pacing or failure of the pacemaker units.

METHODS AND DEFINITIONS

The circumstances surrounding the deaths were ascertained as far as possible from interviews with the relatives and hospital staffs, and examination of record data and police reports.

Sudden death has been recorded when the patient was seen to collapse and die, and when death occurred in bed with no evidence of an attempt to call for help, even though this would have been possible, and without the patient's state giving reason to expect death or there being special circumstances that made sudden death likely

An *autopsy* was performed on 52 of the deceased (84 per cent) 25 of them at Serafimer Hospital, 9 at Karolinska Hospital 6 at the Forensic Medicine Stations, 8 at central county hospitals and 4 at hospitals having consulting pathologists. In all cases they were performed by experienced pathologists. The autopsy records were requested and the results analyzed Only transvenous electrodes situated outside the right ventricle at autopsy were recorded as being dislodged.

The macroscopic arteriosclerotic changes in the coronary arteries were graded as follows

1 *Occasional plaques or no arteriosclerotic changes*
2 *Moderate changes* — Grades between 1 and 3
3 *Calcification* — Severe arteriosclerosis of the coronary arteries, which, however could be divided with a pair of scissors.
4 *Occlusion* — Total occlusion of a coronary artery or arteries, that could not be divided.

The coronary arteries examined were, as a rule, the main trunk of the left coronary artery with the left anterior descending and its circumflex branches, and the main trunk of the right coronary artery with its larger branches.

Myocardial infarction was recorded as recent when, according to histologic examination, it had occurred less than 2 weeks previously

At the *postmortem examination of the generators* the impulse rate and amplitude were determined. If the plastic casing of an implantable generator was cracked or fractured, measurements were generally performed with the generator immersed in water at body temperature. The electrode wires were examined for fracture or damage to the insultation.

RESULTS

MODE OF DEATH

Sudden death — Of the 38 in this group 12 had defective pacemaker units, 9 recent myocardial infarcts and 2 both of these In 6 no autopsy was performed (Table 27)

In the other 9 submitted to autopsy neither pacemaker failure (p 68) nor recent myocardial infarctions (p 70) were found Old infarcts were recorded in 3 and massive coronary sclerosis without infarction in 2. Another had severe aortic stenosis. One patient had massive diffuse fibrosis throughout the

TABLE 27 Mode and causes of death

	No of patients	Per cent
Sudden death	38	61
Heart failure	11(1)	18
Uraemia	4	6
Oliguria or anuria	(3)	
Cachexia	2(2)	
Hypotension or coma	1(4)	
Stroke	2	
Sepsis	1	
Ventricular tachycardia	1	
Angina pectoris	1	
Pneumonia	1	
Total	62	

The figures in parentheses denote the numbers of patients for whom the respective conditions had a bearing on the fatal outcome.

myocardium and only moderate changes of the coronary vessels. One patient with moderate diffuse fibrosis in the myocardium had pronounced narrowing of the left circumflex coronary artery and another degenerative changes of the septal myocardium. The generators of the last 2 patients were not examined at the postmortem check.

To summarize, there was a pacemaker defect in 14 out of the 26 patients dying suddenly where the pacemaker could be checked, while out of the 32 for whom sudden death was recorded and where an autopsy was performed 17 had advanced CHD and 11 of them also recent myocardial infarction.

FAULTY PACEMAKER UNITS

At the time of death external impulse generators (EM 138) were being worn by 37 patients, and an external table pacemaker (Electrodyne prototype) was being used by one 23 had an implanted generator 20 of them operating at a fixed rate (2 EM 137 13 EM 139 5 EM 142) and 3 of them had an atrial-triggered type (EM 141) One patient dying during the operation had never recorded a pacemaker-induced rhythm.

Forty-one generators were checked after the decease of the user and in 2 of these cases no autopsy was performed one of them had an external generator while the implanted generator of the other was removed and the heart was submitted to gross examination. Both these patients died in a hospital having no pathologist. In one patient, whose generator was not checked post mortem, its rate had increased — a sign of voltage drop The defective impulse generators are analyzed in table 28, and defective electrode wires or dislodgements of the endocardial electrodes in table 29 Some form of defect was found in 10 of the 42 generators examined and the one whose rate increased In 6 out of 53 checked the endocardial electrode was dislodged or damaged, or excess wire had been fed in.

In addition, ineffective pacing was recorded in one patient on subsequent inspection of the ECG registered the day she died no autopsy was done and as the generator (EM 138) was not sent for checking it is impossible to say whether the intermittent stimulation was due to generator or electrode failure.

Sudden death was recorded in the case of 12 patients where there was a defective generator or dislodgement of or damage to the endocardial electrode. In a further 2 such cases, failure of the pacemaker was suspected. There was thus confirmation or strong suspicion of defective pacemaker units in 14 out of 38 patients dying suddenly

Generator failure — All 10 patients whose generators were found to be defective post mortem had been paced for at least 6 months — mean 19.1 (±3.1) months

TABLE 28. N mber of impulse generator ber there as an stablished defect or clinical evidenc of ineffecti pacing prior to death 42 nit

	Implanted						
	Fixed rate			Atrial trig	External		
	EM 137	EM 139	EM 142	EM 141	EM 138	Prototype—Electrodyne	Total
Number with defect	1	3	1	0	5	1	11
Total	1	9	3	2	26	1	42

Those whose units were judged to be intact had been paced for on average 11.2 (±2.2) months.

In the case of one patient whose generator was not obtained after his death a defect was suspected

Cas 47 — A man aged 58 years who had been using an implanted generator (EM 137) for 8 months noticed an increasing pulse rate but decided to wait till next day before visiting the doctor the next morning, however, he was found dead in bed. At utopsy minor arteriosclerotic changes in the coronary arteries were found but severe fibrosis in the septum. The pacemaker system was not obtained for checking. In his type of generator a drop in oltage increased the impulse rate.

Altogether 42 pacemaker units were examined post mortem 26 of those were *external* (EM 138) Five were defective (Table 28) 3 gave no impulses owing to capacitor fail ure. In one of these patients the autopsy displayed a picture of subileus from stenosing carcinoma of the colon. One external generator with a fractured casing gave only 0 5 V and one gave 400 impulses/min at the time the patient was brought dead into the hospital. The history in the latter case contains an uncommon complication.

Case 23 — A man aged 45 years with dystrophia myotonica, who had been paced for 3½ years, used an externally worn impulse generator because of poor healing and repeated infection following attempts to implant generators Shortly before death he had taken bath. On admission to hospital the generator was wet and was running at rate of about 400/min. A coupl of hours later when it was dry it functioned properly

Of 9 subcutaneously implanted generators with 5 batteries (EM 139) 3 had cracks in the resin casing that continued into the bat teries they gave 0.6, 0.9 and 1.0 V Of 3 checked implanted generators with 4 bat teries (EM 142) one gave 2.2 V instead of the normal 4.5 V The 2 atrial-triggered generators checked were intact.

The endocardial electrode was found at autopsy to be dislodged in 3 cases and damaged in 2. The former 3 patients had not been paced for more than 2 days before the fatal outcome. In one patient too much wire had been fed down into the right side of the heart and this resulted in tricuspid insuf ficiency and fatal heart failure (p 36)

TABLE 29 Electrode damaged or rongly po itioned discovered on postmortem inspection of 53 electrodes

	No. of failures
Type of defect	
Dislodgement	3
Electrode-insulation defect	
—external	1
—internal	1
Endocardial electrode looping caused insufficiency of the tricuspid alve	1
Total	6

A young man in the material displayed an uncommon complication that deserves a more detailed account.

Case 199 — The endocardial electrode used by 23-years-old man was dislodged after 3 months pacing. A new electrode was spliced on from the neck down to the right ventricle. Severe fibrosis on the right of the neck following the first procedure complicated the second operation and needle was used to force passage through the fibrotic area. About 2 weeks later the patient, after an attack of unconsciousness, appeared at the out patients department. As the heart rate then was regular it was decided to postpone any measures however he died suddenly later the same day. At autopsy it was found that where the wire passed through the fibrotic area in the neck, the insulation was damaged in 2 places for this the needle may have been responsible. There was general advanced interstitial fibrosis of the myocardium.

It is possible that leakage of current reduced the efficiency below that necessary for effective pacing.

Damage to the external electrode was found in case 58.

Case 58 — A woman aged 72 with an external impulse generator (EM 138) suffered from frequent attacks of arrhythmic syncope. At the hospital to which she was admitted ventricular tachycardia was recorded defibrillation was followed by asystole. The heart did not respond to the pacemaker stimuli. Attempts at resuscitation were in vain. Damage to the electrode wire at the connector was subsequently discovered.

HEART WEIGHT

The heart weight was determined in 46 out of the 52 autopsied patients (Table 30). All the hearts weighed more than 300 g. The mean for the 35 men was 605 (±26) g and for the 11 women 460 (±37). In 16 cases the enlargement chiefly involved the left ventricle, in one case the right ventricle and in 7 cases the two ventricles to about the same extent. For the other patients there were no data on the heart configuration.

CORONARY VESSELS

The arteriosclerotic changes were to a large extent uniformly distributed between the left coronary artery and its larger branches on the one hand and the right coronary artery with its branches on the other (Table 31). Only one patient with minor changes in the left coronary artery had the right one occluded. Another had moderate alterations in the right coronary artery and severe in the left.

MYOCARDIAL INFARCTION

Myocardial infarction was demonstrated at autopsy in 3 (44 per cent) of the 52 patients coming to autopsy. Infarcts estimated to be less than 2 weeks old were found in 17. The mean age for the 14 men with recent infarcts verified at autopsy was 78.1 years. Their mean age was significantly higher than that of the patients still alive at the end of the observation period ($P<0.01$).

Nine patients also had older infarcts. In 6 only such were found. Of the infarcts whose position was noted in the autopsy reports, 7 were anterior, 10 posterior and 4 combined anterior and posterior. In 5 patients infarcts in the septum were noted, all old. One patient had an old infarct in the left atrium. The presence of infarcts corresponded closely to the degree of arteriosclerosis. Of the 30 patients dying suddenly and submitted to autopsy 18 had recent or older infarcts or marked coronary sclerosis. Of the 17 patients with a recent infarct 11 died suddenly and of the 6 with old infarcts 3 died suddenly. Of the 6 that had recent myocardial infarcts at autopsy and did not die suddenly one had intense chest pain and died within 30 minutes. Four died from therapy-resistant heart failure. None of them had central chest pains. In 2 of the patients with recent in

TABLE 30 Heart weight at autopsy 46 patients

Heart weight (grammes)	300—399	400—499	500—599	600—699	700—799	≥800	Total
Number of patients							
Women	4	2	3	2	—	—	11
Men	3	5	7	11	3	4	33

TABLE 31 Degree of arteriosclerotic changes in the coronary vessels observed post mortem 50 patients

	Occlusion	Calcification	Moderate changes	Slight or no changes
Left coronary artery with circumflex and left descending branch	3	23	6	18
Right coronary artery with branches	3	23	6	18

farcts there was failure of the generator and one with an old infarct was found at autopsy to have a dislodged endocardial electrode.

MYOCARDIAL FIBROSIS

Of the 52 autopsied patients 5 per cent (31/49) had myocardial fibrosis 12 of them also had infarcts. In one patient with valvular aortic stenosis the fibrosis was located chiefly in the left ventricle in the other cases it was equally extensive on the right and left. In 20 fibrosis had also been seen in the ventricular septum in 4 of these it was found to be more pronounced there than in the rest of the myocardium. One patient with degeneration of the ventricular septum displayed no appreciable changes elsewhere in the myocardium. In one patient with diffuse myocardial fibrosis the fibrous part of the septum was considerably thicker than is normally found.

Nine patients with no sign of myocardial infarction had *fibrosis of the heart muscle and moderate to pronounced occluding arteriosclerosis* their mean age was 72 years 7 were men. Two had defective generators and one tricuspid valve insufficiency owing to too long an electrode wire one had uraemia, one carcinoma of the prostate and one hypotension and oliguria. For the other 3 the cause of death could not be established.

Fibrosis of the myocardium but minor or no arteriosclerotic changes of the coronary arteries — Of the patients without myocardial infarctions but where microscopic examination showed fibrotic or degenerative changes of the myocardium, 10 had at most minor gross arteriosclerotic changes of the coronary vessels one of them was a woman. The mean age of the 9 men was 56 years they were significantly younger than the other autopsied men in the series, 74 5 years ($P<0.01$) The heart weight, determined in 7 of them, was 660 (±63) g, against 595 (±28) g for the other autopsied men the difference is significant ($P<0.001$)

The following causes of death were found in 5 defective pacemaker unit, in one endocarditis with ulceration of an aortic valve cusp followed by severe heart failure, in one marked aortic stenosis with ventricular arrhythmias unaffected by pacemaker

stimulation and leading to death and in one case aortic stenosis and heart failure. Finally one patient died from uraemia of unknown origin and another suddenly without the cause being ascertained

Of the 5 patients in the series with *no fibrosis and at most minor* changes in the coronary vessels 2 are reported above (p 36 and 70) Accounts of the other 3 may also be of interest.

Case 133 — A woman of 84 years with conduction defects of uncertain cause died suddenly fter being paced for 14 months. The epoxy resin of the generator was found to ha been fractured and the voltage had dropped to 0 6. Only minor arteriosclerotic plaques were seen i the coronary essels.

Case 161 — A woman ged 70 years with Sjögren s disease uraemia, severe emaciation d ring 8 months pacing her general cond tion had gradu lly deteriorated. Autopsy disclosed a tumou 3 cm across, in the hypophysis, and slightly smaller one in the A V node (p 73) Microscopic examination of the tumou revealed a granulomatous mass with necrotic reas, numerous eosinophilic cells, giant cells and lymphocytes (Fig. 13)

Case 189 — A man ged 60 years w th alternately conducted and non-conducted heart rhythm, and arrhythmic syncope suffering from increasi g heart failure and severe emaciation. A pacemaker was provided He died 2 months later from heart failure At autopsy multiple carcinoids of the small intestine were found, with metastases in the lungs, myocardium, sinus node A V node and the bundle of His

No evidence of fibrosis — In respect of 4 patients the autopsy reports contained no annotations on the occurrence of fibrosis in the heart muscle. One of them, who was found dead in bed, had ileus due to carci noma of the colon, and at autopsy the pacemaker was not functioning In another the electrode wire had dislodged The third who had died suddenly had severe arteriosclerotic changes of the left coronary artery

No aut psy — Of the 10 patients not submitted to autopsy 2 mentioned above displayed signs of generator failure, 2 had histologically confirmed carcinoma at operation, one pulmonary carcinoma, one ventricular carcinoma with metastases in the regional lymph nodes and liver and 2 severe heart failure Of the other 4 all of whom died suddenly one had invalidizing angina pec toris, wh le one with an atrial-triggered generator had moderate heart failure.

OTHER OBSERVATIONS AT AUTOPSY

Thrombi around the transvenous electrode were seen in the superior vena cava in one patient and in the right atrium in another One of these 2 also had endocarditis of the tricuspid valve. One of the autopsied patients had pulmonary emboli and thrombi in the pulmonary artery but not around the elec trode.

In one of the deceased the electrode wire was found at autopsy to pass through one of the tricuspid cusps, but there were no clinical signs of tricuspid insufficiency

Two patients had endocarditis in the aortic valves. Marked aortic stenosis was found in one patient. Another patient dying from heart failure had a bicuspid aortic valve with endocarditic scarring in the cusps.

DISCUSSION

The term dislodgement has been applied here only when the transvenous elec trode was found outside the right ventricle, thus excluding the cases where its position had been disturbed at autopsy Theoretically this might also include electrodes lying free in the right ventricle *in vivo* but in practice this is unlikely as this position generally gives intermittent stimulation, with symptoms that would prompt the patient to con sult a doctor It cannot be ruled out that there was generator failure in the case of a

Figure 13 Granulomatous myocarditis areas of necrosis, giant cells, numerous eosinophilic leukocytes, some lymphocytes (Case 161)



few of the 21 impulse generators not examined post mortem

Sudden death occurred 6 of the 10 patients not autopsied and 61 per cent of all the deceased in this respect there was thus no difference between the autopsy and nonautopsy groups Most of the sudden deaths occurred in patients found at autopsy to have recent infarcts or faulty pacemaker units.

The two defects most commonly found in the pacemaker units at the postmortem examination were fracture of the epoxy resin casing of the implanted generator with arrested function or essentially reduced voltage, and dislodgement of the transvenous electrode. The patients with defective generators were found post mortem to have been paced a shorter time than those where the checking disclosed no defects. Technical failures were also common in Harris series[49]

of paced patients examined post mortem — in 11 out of 26 such patients.

It is well established that stimulation in the vulnerable period of the heart cycle can gi e rise to ventricular tachycardia and fibrillation[19 200 214]. That coronary ischaemia depresses the threshold for these arrhythmias by a factor of 5 to 10 has been demonstrated experimentally on laboratory animals[29 225] and likewise that after ligation of a major coronary artery the vulnerable period is almost invariably followed by ventricular fibrillation, even though the stimulating electrode is located at a distance from the experimentally produced ischaemic zone[43] thus even stimulus nitiated by an atrial electrode and falling into the vulnerable period was found to lead to ventricular fibrillation.

Siddons & Sowton[196] have compiled 25 reports in which ventricular fibrillation was registered during pacing In 5 of the 35 deceased patients infarcts were found In the present study a statistical correlation was found between the occurrence of CHD and VEB (p 58) It seems likely in the case of at least some of the deceased that these two factors together were responsible for the fatal outcome.

The larger the electrode tip the weaker the stimulus required to induce ventricular fibrillation[42] In 1967 the area of the electrode tip of the Elema transvenous electrode was changed from 65 to 45 mm[2]

The pacing time was not shorter for the patients with a recent nfarct at autopsy than for those without. A posterior location of the myocardial infarction in patients with CHB has been found to be over-represented by among others, Johansson[102] Among the conf rmed cases of myocardial infarction in the present series this location was not more common than an anterior one.

Only one of the patients with a recent myocardial infarction at autopsy had suffered from chest pains None of the 23 in whom infarcts were found at autopsy had been admitted to hospital during pacing with a diagnosis of confirmed or suspected infarction In spite of this, 18 of them had infarcts less than 2 weeks old. In some of them the fatal outcome was preceded by increasing heart failure

Sudden death might be the sole manifestation of myocardial infarction. In a Swedish study of autopsied patients dying outside hospital, recent myocardial infarcts were recorded as the initial symptom of CHD[226] in about 20 per cent of the males over 50 The same proportion of cases with a sudden death as the first manifestation of CHD was found in the Framingham study[207] however most of the recent infarcts in the present study were at least a few days old.

It has been considered that the clinical symptoms are less severe in the elderly with myocardial infarction[207] The men found at autopsy to have recent myocardial infarction were also older than any of the men in the present series.

The men with myocardial fibrosis and no appreciable changes in the coronary arteries were younger and had on average a higher heart weight than the other autopsied men. Both defects in the pacemaker system and aortic valvular heart disease were common in these patients. It is possible that in some of them the myocardium was in such a poor state that pacemaker failure resulted in fatal arrhythmia. In the case of those with aortic valvular heart disease and marked myocardial fibrosis it is instead possible that the arrhythmias prompting the decision to introduce pacing may have been a manifestation of such serious myocardial insufficiency that the pacing was n vain.

An analysis was made of the deceased with respect to age, sex, duration of pacing, the existence of other diseases than conduction defects, heart size, the arrhythmias causing syncope, the clinical features of the attacks of arrhythmic syncope before pacing and types of arrhythmias before and during pacing. Some of these observations have been compared with those at autopsy

RESULTS

The age at the implantation of the electrodes in the 62 deceased patients ranged from 25 to 90 years, with a mean of 68 5 Forty four were men — constituting 28 per cent (44/159) of all men paced at the end of observation period — and 18 were women, the corresponding percentage being 20 per cent (18/89) The sex difference in mortality is not statistically significant. The mean age of the deceased men was 68 9 years, against 64.8 years for the living men. The corresponding figures for the women were 67 6 and 64.3 years, respectively the age *differences are not significant.*

The duration of pacing *via* endocardial electrode wires before the fatal outcome ranged from 24 hours to 71 months, with a mean of 15 (±2 4) months thus does not include the time during which, in 3 of the deceased, epicardial electrode wires were used until their replacement by transvenous ones (Fig 6) The mean pacing time for those still using the pacemaker at the end of the observation period was 26 (±1 3) months.

Most of the patients died early during the period of treatment (Fig 14) — 16 per cent (10/62) of the deceased died within one month of the introduction of pacing Three of them had a dislodged endocardial electrode, 2 severe aortic stenosis and one an old infarct at autopsy while one died from aortic valve endocarditis associated with sepsis. The sole patient dying during the operation is reported on page 36.

INDICATIONS

The indications for the pacing in the 62 deceased in relation to those for the whole material are shown in table 32. Arrhythmic syncope was recorded in 94 per cent (58/62) of the deceased compared with 87 per cent (162/186) of the living that were still being paced on 31st March, 1968 the difference is not significant. The case history for one of the deceased patients who did *not* have arrhythmic syncope before the pacing has been presented above (p 36) The other 3 patients died from causes unrelated with the pacing 2 of them had

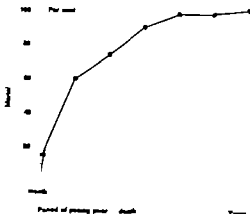


Figure 14 Period of pacing prior to death

TABLE 32. Indications for pacing in the case of patients subsequently dying and those still alive and using a pacemaker at the end of the observation period

	Deceased		Alive	
	No. of patients	Per cent	No. of patients	Per cent
Arrhythmic syncope	49	79	140	75
Severe heart failure+A.S.	7	12	15	8
no A.S.	2	3	4	2
Low working capacity+A.S.		3	7	4
no A.S.	0		11	8
Other indications		3	6	3
Total	62	100	186	100

TABLE 33. Heart rhythm before pacing in the case of patients subsequently dying and those still using a pacemaker at the end of the observation period

	Deceased		Alive	
	No. of patients	Per cent	No. of patients	Per cent
Constant sinus rhythm, A.V. block I or II	8	13	14	8
Constant complete heart block	20	32	65	35
Variations between sinus rhythm, A.V. block I or II and idioventricular rhythm	34	55	107	57
Total	62	100	186	100

severe heart failure combined with CHB before the pacemaker was furnished, and both died from heart failure despite pacing, digitalis and diuretic therapy. The fourth died from uraemia.

ECG FINDINGS

The ECG findings before pacing in the case of the deceased are presented in table 33. Permanent complete heart block was found in 32 per cent (20/62), various conduction defects in 55 per cent (34/62) and conducted rhythm, alone, in 13 per cent (8/6).

VEB were found before pacing in 61 per cent (38/62) of those dying during stimulation, against 38 per cent (71/186) of those still paced at the end of the observation period; the difference is significant ($P<0.01$).

Atrial fibrillation or flutter, either constant or intermittent, was found before introduction of pacing in 30 per cent of the deceased group (18/60) against 11 per cent (21/184) of the living patients; the difference is significant ($P<0.01$).

ECGs were recorded during arrhythmic syncope before pacing in 48 per cent (30/62) of the deceased and 48 per cent (89/186) of those living and being paced at the end of the observation period. PVTA was recorded in 13 of the 30 deceased, in 6 of whom asystole was also recorded, and in

TABLE 34 Heart rhythm during pacing in the as f patient sub equently dying nd the still al and ting pacemaker at the end of the observatio period

	Deceased		Alive	
	No. of patients	Per cent	No. of patients	Per cent
Regula paced rhythm	24	39	100	54
Competition	18	29	69	37
VFB during pacing	18	29	17	9
Total	60	97	186	100

24 of the 89 survivors the difference is not statistically significant Asystole alone was recorded in 17 of the 30 deceased where ECGs had been registered during the attack of arrhythmic syncope, against 73 per cent (65/89) of the living still being paced at the end of the observation period.

ECGs registered during pacing were available for all but 2 of the deceased (Table 34) The number of patients with VEB dur ing pacing was significantly higher for the deceased (18/60) than for the rest of the material (17/186) ($P<0.01$) The 18 deceased where VEB were recorded during pacing comprised 12 out of the 23 with myocardial infarction confirmed histologi cally 4 out of the 28 submitted to autopsy with no infarction, and 2 not autopsied VEB were significantly more common among the deceased with than without confirmed infarction ($P<0.01$)

ATTACKS OF UNCONSCIOUSNESS BEFORE AND DURING PACING

Unconsciousness during pacing occurred 19 of the 52 deceased (37 per cent) where there were relevant data, against 34 out of 180 living (19 per cent) that had a pacemaker at the end of the observation period the difference is significant ($P<0.01$)

During the attacks of arrhythmic syncope before the pacing 16 of the deceased had had convulsions and/or passage of urine or faeces, while 2 suffered from cerebral confusion after attack. These signs of protracted attacks were not significantly more common in the deceased than in the rest of the series. On the other hand, attacks of long duration before pacing were more commonly registered among those who died during the pacing than among those still alive at the end of the observation period (p. 58)

The pacing time for the 12 deceased where resuscitation measures were taken before stimulation ranged from 2 days to 36 months, with a mean of 14 months. Three of them were paced for less than 5 days one was a woman of 65 years with recorded attacks of ventricular tachycardia during pacing she died suddenly and at autopsy an old myocardial infarction was found. The other 2 were a man of 47 with cardiomyopathy where dislodgement of the electrode was disclosed at autopsy and a man of 86 with both asystole and ventricular fibrillation during implantation of the endocardial elec trode, and postoperative hypotension he died after 3 days pacing, and the autopsy produced no evidence of arteriosclerotic heart disease or failure of the pacemaker system. The other 9 i this group were paced for at least 2 months.

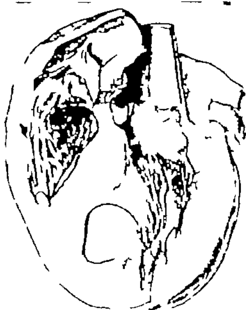


Fig. 15 Massive hypertrophy of the interventricular septum bulging into the right ventricle (Case 85)

OTHER DISEASES THAN CONDUCTION DEFECTS

Angina pectoris was recorded in 28 per cent (16/58) of the deceased where an evaluation could be made, against 15 per cent (26/173) for those still paced at the end of the observation time this difference is significant ($P<0.05$) Of the 16 autopsied patients with angina pectoris 10 had myocardial infarction, one severe and one moderately severe arteriosclerosis in the coronary arteries In the other 4 patients no autopsy was performed (p 67) The frequency of angina pectoris was significantly higher in the patients with histologically confirmed myocardial infarction (7/13) than in the living (28/198) ($P<0.01$) Of the 23 patients with verified infarction (p. 70) only one had such severe central chest pains before pacing was begun that she consulted a doctor a diagnosis of infarction was made. One patient with verified infarction presented a classical picture of infarction with retrosternal chest pains *during* pacing. The age at the time the pacemaker was implanted in the 16 deceased patients who had had angina pectoris was 72 4 years and for the 28 living with angina pectoris, 65 5 years the difference in age is significant ($P<0.01$)

Diabetes occurred in 13 per cent (8/62) of the deceased and in 10 per cent (19/186) of those living and using a pacemaker at the end of the observation period

The diastolic blood pressure recorded just before the pacing was, on average, 84.2 mmHg for the deceased and 84 6 mmHg for the whole series.

Severe heart failure during pacing was more common among the deceased than in the rest of the series — 65 per cent (37/57) against 35 per cent (67/193) this difference is significant ($P<0.01$)

In 5 of the deceased myocarditis had been suspected. Autopsy disclosed old pericarditis in one and suspected old myocarditis in one, while another had scattered degenerative areas in the heart muscle that might have been due to earlier myocarditis The other 2 patients did not come to autopsy

Of the 8 patients in the series with hereditary cardiomyopathy one died (Fig 15) at autopsy dislodgement of the endocardial electrode was found

Aortic valvular heart disease was found in 6 of the 62 deceased 3 of them had a narrow stenosis and one muscular subaortic stenosis. In the rest of the series there were 12 cases of aortic valvular heart disease One of the patients with both mitral stenosis and insufficiency died.

Rheumatoid arthritis was found in 4 of the deceased and in 7 of the rest of the series. Uropolyarthritis was found in 2 of the deceased out of a total of 10 with this condition.

DIGITALIS THERAPY

Continuous digitalis therapy during pacing was given to 60 per cent of the deceased (36/60) against 41 per cent of those living and being paced at the end of the observation period (75/184) the difference is significant ($P<0.01$)

As regards those patients dying suddenly with neither recent myocardial infarction nor a defective pacemaker unit, there was no difference between those receiving digitalis (5 out of 18) and those not (3 out of 14)

DISCUSSION

The differences obtained for some of the factors studied in the deceased and the living patients at the end of observation period might have been greater if the observation times had been of the same length. As most of the deceased died suddenly and outside hospital the observation of these just before the death was probably not more thorough than for the others this might otherwise have accounted for some of the differences

The anamnestic data were not so complete for the deceased as for the living, since only a few of them were alive at the follow-up examination conducted in the autumn of 1967 As all were at hospital before and/or at the time of the implantation of the electrodes most of the required information was to be found in their records. I the case of 2 of the deceased, however no ECG registrations were made during the pacing.

The outcome for unpaced patients with CHB has been found to vary with the cause of the block[80, 89, 103, 158] and the presence and the extent of other damage to the heart than the A V block[85, 80, 103] I 60 paced patients Karlson and co-workers[111] found a close correlation between the fatal outcome and severe heart-muscle damage, manifested prior to death as heart failure. The higher frequency of heart failure, VEB and atrial fibrillation or flutter in the deceased than in the living at the end of the observation period in the present material probably reflects a higher frequency and greater severity of myocardial damage in the deceased The fact that digitalis therapy was more common among the deceased than the living points to a greater frequency of myocardial failure among the former On the other hand, it would seem that the depressing effect on the ventricular automaticity shown to be associated with digitalis (Section XIV) had no appreciable bearing on the frequency of a fatal outcome in this series for then the proportion with digitalis therapy would have been greater for those dying suddenly and having either a defective pacemaker system or recent myocardial infarction than for the other patients, and this was not the case.

Arteriosclerosis of the coronary arteries was common in the deceased group — probably more common than among the living, since the frequency of angina pectoris among the deceased with no pacemaker defect was greater than in the rest of the series. The frequency of myocardial infarction found at autopsy was also high.

The high mortality during the first month of treatment in this series was due to the fact that some of the patients with severe myocardial damage died early from heart failure, that patients with severe renal complications died early and that those where there was dislodgement of the electrode w re at autopsy died shortly after pacing had been introduced

The frequency of patients with a silent myocardial infarction was higher than in a number of infarction series[141, 182, 210] The frequency of diabetics was no higher among the deceased than for the whole material.



Figure 13 Massive hypertrophy of the interventricular septum bulging into the right ventricle (Case 83)

OTHER DISEASES THAN CONDUCTION DEFECTS

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Rheumatoid arthritis was found in 4 of the deceased and in 7 of the rest of the series. Uropolyarthritis was found in of the deceased out of a total of 10 with this condition

XIII REHABILITATION OF PACED PATIENTS

by

O Edhag & E. M. Wedelin

To elucidate the effect of pacing on some of the mental and physical conditions of the patients beyond what has been mentioned above, and on their social situation and their attitude to pacing, an interview study was carried out. Information was also obtained from the National Health Insurance records

MATERIAL

The interviewed subjects comprised all the living patients that had been provided with endocardial electrodes at the Department of Thoracic Surgery Karolinska Hospital, up to 1st J ly 1966, with the exception of those in which the pacing had been terminated in addition, 4 patients with epicardial electrodes (nos. E 17—20 p 17) were included. They numbered 139 of whom 85 were men and 54 women their mean ages were 66.6 and 65 5 respectively The chief indication for pacing was arrhythmic syncope, which was registered in 82 per cent (114/139) in 5 cases severe and in 5 moderately severe heart failure had a bearing on the decision to introduce pacing. Eleven per cent (15/139) of the series had not had arrhythmic syncope f gure that is not significantly different from that for the whole material (p 51) the indications for pacing were moderate heart failure combined with CHB and a slow ventricular rate (12 patients) severe heart failure and CHB (2 patients) and A V block II and VEB (1 patient) At the time of interview 83 per cent (115/139) of the patients had fixed rate impulse generators and 17 per cent (24/139) the atrial-triggered type. The fixed rate generator was subcutaneously implanted in 47 per cent (54/115) and worn externally in 53 per cent (61/115)

The interviews were performed at the earliest 3 and at the latest 70 months after the patients had received their pacemaker units they had been paced for an average of 26 months before the interview

The interviewed patients were divided into 2 groups according to whether they had or had not reached 67 years — the age at which Swedes qualify for receipt of the national basic pension. The distribution by age groups and type of generator are shown in figure 16 The time the patients were incapacitated before pacing ranged from less than 24 hours to about 10 years. Eleven patients received their pacemaker un ts less than 2 weeks after the onset of A V block or arrhythmic syncope. Twenty patients had had moderate heart failure with a low physical capacity for less than one month, 34 for less than 12 months and 2 for about 10 years prior to pacing For those handicapped for more than one week before pacing the mean period was 23 months.

METHOD

The interviews were performed on the occasion of the checks of the pacemaker units at the Department of Internal Medicine, Serafimer Hospital — with the exception of 5 patients for whom it was carried out at their homes. At the interview standardized questions were put orally by a wel

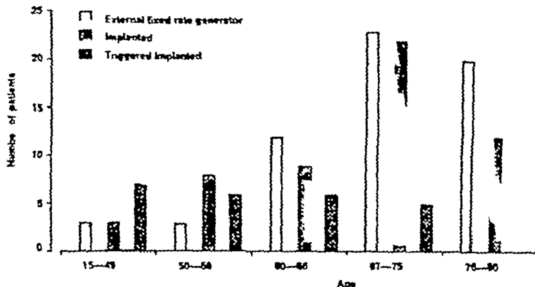


Figure 16 Type of impulse generator by age 139 interviewed patients.

fare officer experienced in this type of study[23]. In a few cases where the patients found it impossible to answer certain questions, information was obtained from relatives.

To obtain a general view of the patients own experience of the pacing they were asked whether they felt better, worse or the same after the introduction of pacing. Those in gainful employment were asked how long they had been working and whether the work was heavy, moderately heavy or light. The women were asked whether they could usually manage without assistance with the laundry work, cleaning, shopping and preparing meals. An analysis was made of the extent to which the patients required daily help or supervision at home or were admitted to institutions before and during the pacing.

The patients were asked how well they could manage walking on level ground and climbing stairs.

From the Offices of the National Health Insurance, of which every Swede is a member, information was requested by mail on how long the patients had been admitted to hospital for heart disease, dizziness or arrhythmic syncope, and on account of a surgical operation or examination concerned with pacing. For the 80 patients for whom information was obtained from the Insurance Offices the total time elapsing between the first admission to hospital on these grounds and the introduction of pacing was 1703 months, against 2990 months for admissions *during* pacing. The mean time in hospital before pacing was corrected with respect to the time during pacing.

Note was made of the number of persons granted a retirement pension on grounds of illness and whether this was done before or after application of a pacemaker.

The patients with external impulse generators (EM 138) were asked how they managed their hygiene, since these generators were not water-tight. Those with this type of impulse generator at the time of the

TABLE 35 Patients' views on the effect of pacing

	Improved	Unchanged	Worse	No opinion
Age				
15—66	41	12	4	0
67—90	61	11	6	4
Total	102	23	10	4
Per cent	73	17	7	3

interview were also asked whether they would like to change to a subcutaneously implantable generator

Possession of a driving licence was recorded and the patients were asked whether they were using a car

RESULTS

SUBJECTIVE EXPERIENCE OF PACING

Most of the patients — 73 per cent — experienced an improvement, 17 per cent felt no improvement and 7 per cent felt worse since the pacing was begun 3 per cent could not express an opinion (Table 35) There was no significant difference in the proportion of improvements between patients over and those under 67 years — 74 per cent (61/82) and 72 per cent (41/57) respectively — nor between patients with fixed-rate and triggered generators, with 74 (85/115) and 71 per cent (17/24) respectively Four patients with atrial-triggered units stated that there had been a marked improvement since the change from fixed-rate to triggered stimulation.

From the patients comments to the enquiry as to their impression of the value of the pacing an attempt was made to establish the grounds for their views. The comments could be assessed in 87 per cent (89/102) of those reporting an improvement In 60 per cent (53/89) of them the motivation was that they had had no attacks of arrhythmic syncope and hence been rid of the fear of fainting and injuring themselves. For about a year before the start of pacing 2 of these patients had been practically confined to bed — from fear of falling and injuring themselves in connection with arrhythmic syncope rather than through physical restriction. Seventeen per cent (15/89) of those finding an improvement considered that the pacemaker had saved their lives An increase in physical capacity was regarded as the chief benefit of the pacing by 23 per cent (21/89) of the patients — by 4 because they no longer suffered from incapacitating respiratory distress. Five in this group considered that the freedom from attacks contributed to an improvement after pacing was begun.

Of the patients finding no change, or even a deterioration, in their condition some had had arrhythmic syncope only a day or so before they received the pacemaker system, some had had other invaliding diseases than conduction defects and some had had arrhythmic syncope or an annoying feeling of arrhythmia during the pacing. One of those believing that her condition had worsened had a cervical plexus lesion, with partial paresis of the right arm, in connection with complicated insertion of the transvenous electrode (p 36) Another of the patients feeling worse had invaliding vertigo induced by streptomycin, which had

TABLE 36. Gainful employments distributed by full/part time and strenuousness 40 patients

	Heavy	Moderate	Light		Total	
			Men	Women	Men	Women
Full time work	5	7	13	1	25	1
Part time	3	3	4	4	10	4
Total	8	10	17	5	35	5

been given for infection around an epicardial electrode before changing to endocardial pacing.

At the beginning of pacing, sometimes for several months, a number of the patients found it difficult to rely on their pacemaker units even though they functioned perfectly Occasionally their anxiety was to some extent justified by disturbances in pacing. Some found it difficult to rid themselves of the idea that experienced ectopic beats or competition were due to failure of the pacemaker unit these thoughts came particularly at nights several suffered from insomnia. Many had functional symptoms At the time of the follow up examination 32 per cent of the patients were regularly taking sedatives or psychopharmacologic agents (p 32)

GAINFUL EMPLOYMENT

Of the 139 patients interviewed 29 per cent (40/139) were working, 5 of them women (Table 36) Ten of them were over 67 years *Of the 57 patients below pensionable age* 51 per cent were working (29/57) Among the other 28 there were 9 women who were capable of managing their domestic work. Sixteen of the patients over 67 years were drawing a disablement or retirement pension The remaining 3 were women for 2 of them a disablement pension had been applied for but not yet been received one of these had diabetes with vascular complications, and the other had severe impairment of vision. One woman with bronchial asthma had a short time left before she could draw her old age pension, and she therefore did not apply for a disablement pension.

When they had received their pacemaker units all but of the gainfully employed returned to their original jobs One of them, a factory employee with an atrial triggered generator tried to find a factory with less electrical apparatus that could interfere with his pacemaker than the one where he had been employed previously The other was a female shop assistant who was retrained for a less stressing secretarial job while she was using a pacemaker Nervous symptoms and moderate hypertension were contributory reasons for her change of work. Among the 40 gainfully employed there was a trombonist, who was granted a disablement pension because of complete heart block with a low ventricular rate before pacing was introduced, but who afterwards was able to resume *his profession. The youngest patient in* the series was still at school when he received the pacemaker electrodes, but at the time of the interview he had started a business.

The work of 8 of the 40 employed patients (Table 36) was classed as heavy Five were working full-time This group included a farmer a master gardener a fisherman, a labourer and a warehouse em-

TABLE 37 Gainful employment and need of assistance before and after pacing, 83 men

	Gainfully employed	Not gainfully employed amount of assistance		
		None	Occasional	Daily
Age				
15—66 Before pacing	22	1	7	4
During	24	2	8	—
67—90 Before pacing	1	3	26	10
During	10	4	19	8
Total Before Pacing	34	4	33	14
During	34	6	37	8

ployee A report relating to one of these patients may be of interest in this connection.

Case 7 — *A farmer aged 33 He did not consider* that the external impulse generator (EM 158) interfered with his work, even though he was *obliged to take rests more often than his* fellow workers. With a fixed pacing rate of 72 impulses/min he could carry 75 kg sacks and walk fairly long distances in snow some 20—30 cm deep. In an exercise test on the cycle ergometer he managed 6 minutes at 300 kgf m/min, 6 minutes at 600 kgf m/min and one minute at 900 kgf m/min, before he stopped through shortness of breath

Ten of the patients were doing work classed as moderately heavy they included *factory workers shop assistants*, electricians, a musician and dentists Neither of these 2 groups contained women The patients doing physically light work numbered 21 including one woman on full time and 4 on part time They included secretaries, *civil servants* messengers, directors and engineers

NOT GAINFULLY EMPLOYED

Of the 10 men not engaged in gainful employment and below pensionable age at *the time of the interview 2 were receiving* retirement pensions (Table 37) Six of the other 8 had a conduction defect together with invalidizing diseases such as aortic valvular *heart disease, angina pectoris, adiposity* and mental backwardness. For none of the men under pensionable age who were working, though not full time, was the pacing the limiting factor One of those on part time had severe aortic insufficiency while the restriction of the others working capacity was due to extracardial causes.

As regards the women over pensionable age not in gainful employment there were no significant differences in respect of their activities before and during pacing (Table 38) Of those below this age, 4 that had not performed any domestic work before receiving the pacemaker were now capable of doing so these women had been incapacitated for 2—5 years before pacing In the case *of 5 of the 8* women that, *after* implantation, could not do any household work at all or required some help daily there were complicating invalidizing diseases, namely diabetes and heart failure, severe arthritis *of the* knee joints, Parkinson's disease, senile dementia and paralysis of an arm owing to plexus injury The ages of the other 3 women were 80 78 and 73 years

Equivalent to *kilopond meter/min* (kp m/min)

TABLE 36 Gainful employment distributed by full/part time and strenuousness in 40 patients

	Heavy	Moderate	Light Men	Light Women	Total Men	Total Women
Full time work	5	7	13	1	25	1
Part time	3	3	4	4	10	4
Total	8	10	17	5	35	5

been given for infection around an epicardial electrode before changing to endocardial pacing

At the beginning of pacing, sometimes for several months, a number of the patients found it difficult to rely on their pacemaker units, even though they functioned perfectly Occasionally their anxiety was to some extent justified by disturbances in pacing. Some found it difficult to rid themselves of the idea that experienced ectopic beats or competition were due to failure of the pacemaker unit these thoughts came particularly at nights several suffered from insomnia. Many had functional symptoms At the time of the follow-up examination 32 per cent of the patients were regularly taking sedatives or psychopharmacologic agents (p 52)

GAINFUL EMPLOYMENT

Of the 139 patients interviewed 29 per cent (40/139) were working, 5 of them women (Table 36) Ten of them were over 67 years Of the 57 patients below pensionable age 51 per cent were working (29/57) Among the other 28 there were 9 women who were capable of managing their domestic work. Sixteen of the patients over 67 years were drawing a disablement or retirement pension The remaining 3 were women for 2 of them a disablement pension had been applied for but not yet been received one of these had diabetes with vascular complications, and the other had severe impairment of vision One woman with bronchial asthma had a short time left before she could draw her old age pension, and she therefore did not apply for a disablement pension.

When they had received their pacemaker units all but of the gainfully employed returned to their original jobs One of them, a factory employee with an atrial-triggered generator tried to find a factory with less electrical apparatus that could interfere with his pacemaker than the one where he had been employed previously The other was a female shop assistant who was retrained for a less stressing secretarial job while she was using a pacemaker Nervous symptoms and moderate hypertension were contributory reasons for her change of work. Among the 40 gainfully employed there was a trombonist, who was granted a disablement pension because of complete heart block with a low ventricular rate before pacing was introduced, but who afterwards was able to resume his profession. The youngest patient in the series was still at school when he received the pacemaker electrodes, but at the time of the interview he had started a business.

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Total Before Pacing	34	4	33	14
During	34	6	37	8

ployee. A report relating to one of these patients may be of interest in this connection.

Case 7 — A farmer aged 33 He did not consider that the external impulse generator (EM 138) interfered with his work, even though he was obliged to take rests more often than his fellow workers. With fixed pacing rate of 72 impulses/min he could carry 75-kg sacks and walk fairly long distances in snow some 20—30 cm deep In an exercise test on the cycle ergometer he managed 6 minutes at 300 kgf m/min, 6 minutes at 600 kgf m/min and one minute at 900 kgf m/min, before he stopped through shortness of breath

Ten of the patients were doing work classed as moderately heavy they included factory workers, shop assistants, electricians, musician and dentists Neither of these 2 groups contained women. The patients doing physically light work numbered 21 including one woman on full time and 4 on part time. They included secretaries, civil servants, messengers, directors and engineers.

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Of the 10 men not engaged in gainful employment and below pensionable age at the time of the interview 2 were receiving retirement pensions (Table 37) Six of the other 8 had a conduction defect together with invalidizing diseases such as aortic valvular heart disease, angina pectoris, adiposity and mental backwardness. For none of the men under pensionable age who were working, though not full time, was the pacing the limiting factor One of those on part time had severe aortic insufficiency while the restriction of the others working capacity was due to extracardial causes.

As regards the women over pensionable age not in gainful employment there were no significant differences in respect of their activities before and during pacing (Table 38) Of those below this age, 4 that had not performed any domestic work before receiving the pacemaker were now capable of doing so these women had been incapacitated for 2—5 years before pacing In the case of 5 of the 8 women that, after implantation, could not do any household work at all, or required some help daily there were complicating invalidizing diseases, namely diabetes and heart failure severe arthritis of the knee joints, Parkinson s disease, senile dementia and paralysis of an arm owing to plexus injury The ages of the other 3 women were 80 79 and 3 years.

Equivalent to *kilopond meter/min* (kp m/min)

TABLE 38 Gainful employment and household duties before and after pacing 34 women

			Assistance in household duties				
		Gainfully employed	None	Some	All except cooking	Usually in all duties	Help needed for personal hygiene
Age							
15—66	Before pacing	6	4	2	6	4	1
	During	4	6	3	9	—	1
67—90	Before pacing	1	9		13	2	4
	During	1	7	4	12	3	4
Total	Before pacing	7	13	4	19	6	5
	During	5	13	7	21	3	5

DISABLEMENT PENSION

Disablement pensions with heart disease as the sole, or contributory ground were received by 11 patients before and 13 during the pacing. Of these 24 patients receiving a disablement pension 14 were still under pensionable age at the interview. The youngest of them was a woman of 29 years with hereditary cardiomyopathy who was granted a disablement pension 12 months before pacing was introduced; the others were over 48. The mean ages of the patients granted a disablement pension before and during pacing were 53.3 and 61.2 years, respectively.

In most of the patients conduction defects were the chief heart affections; others had valvular heart disease, cardiomyopathy and cardiosclerosis. The resistance to, or apprehensions at the prospect of, returning to work after long illness, and difficulty in finding a suitable job were among the factors prompting application for a disablement pension during pacing. The musician mentioned above was granted a disablement pension owing to complete heart block 7 years before receiving the pacemaker that enabled him to resume his musical career; the pension was then withdrawn. At the time of the interview he had been working for 5 years using the pacemaker. One paced patient who applied for a disablement pension was refused. Five patients had been granted a disablement pension on grounds other than the heart disease.

Four patients were drawing retirement pensions when pacing was begun or they were granted subsequently.

NEED OF ASSISTANCE

As is seen in tables 37 and 38, there were only a few patients that, before pacing, required daily help, some of them with supervision, and that were admitted to a nursing home. In the case of 4 male patients there was a marked difference between their need for supervision before and during pacing. They had all been in hospitals for more than 3 months prior to the electrode implantation, one for about 12 months, but during pacing they could manage at home.

The 5 women requiring daily help and admitted periodically to hospitals before pacing required help to the same extent afterwards. All had invalidizing extracardial diseases.

duction defect and arrhythmic syncope shall report to the county medical officer or the *first municipal medical officer* Only 3 of the 53 patients with driving licences had had it withdrawn before pacing 2 of them received t back after the introduction of pacing. One of these patients was required by the County Administrative Board to present each year a medical certificate issued by a heart specialist. Two patients had had their licence to dri e commercial vehicles with drawn after introduction of paci g The others were granted a certificate of health to obtai a driving licence while using a pacemaker their applications had been sanc tioned by the National Board of Health and Welfare. To possess a driving licence these 2 patients were required to undergo regular medical examinations, and every year to pre sent a certificate of health issued by a heart *specialist.*

Of the 52 patients in possession of a driv ing licence at the interview — 37 per cent of the number interviewed — 6 drove a car 14 of them at least 5 times a week. Three considered that they were dependent on havi g a driving licence in order to pursue their occupation. Of those possessing a driving licence that did not drive a car several had been recommended by a doctor not to do so Eight of the 26 that drove a car had had attacks of arrhythmic syncope during pacing, and as many there had been at least one occasion when the pacemaker unit had not functioned properly None of the patients reported accidents i connection with driving while using a pacemaker

DISCUSSION

The mean age for the 139 patients inter iewed — 65 years — was about the same as that for the whole series. Nor was there any significant difference between the ratio of women to men in the two groups — *54/85 for the interviewed and 94/166 for* the whole material.

As regards the indications for pacing there was no significant difference between the interv ewed group and the whole series with an endocardial electrode Arrhythmic syncope was the sole indication in 82 per cent of the patients receiving a pacemaker unit up to 1st July 1966 — that is, of the interviewed group — against 75 per cent for the whole series. Of the 25 patients having no attacks of arrhythmic syncope before pacing 15 were in the interviewed group Of the 45 patients receiving a pacemaker before 1st July 1966, and not interviewed, 38 had died and in 7 the pacing had been discontinued This may have affected the selection, n that some of the most severely *i validized were lost to the study However* most of those dying from an extracardial cause did so suddenly It is thus improbable that the clinical picture for those dying be fore the interview differed from that of the interviewed group

On 31st March, 1968, external generators (EM 138) that were not watertight were worn by 44 per cent of the interviewed against 21 per cent for the whole material this difference is d e to the fact that the patients to receive a pacemaker most recently and not interviewed were recommended more strongly and a greater number ac cepted, to have an implanted generator An other point is that the ventricular-triggered impulse generator was introduced after the terviews, and the atrial triggered one had become more common This may have had a bearing on the number of patients experiencing arrhythmia during the pacing.

So that the study should be as objective as possible the questions were standardized.

To avoid any influence from the patients attitude to the hospital medical staff the interviews were conducted by a welfare officer with whom they had not previously come into contact. In the space of the 3 months or more that elapsed between the implantation and the interview the patients had probably been able to form an opinion of the implications of the pacemaker for them.

By virtue merely of the fairly regular medical check-ups that the patients were bound to have some of them probably felt more secure Moreover other diseases than conduction defects appeared after pacing had been started whether this fact affected their experience of the pacing is difficult to say The existence of other factors, including financial position, availability of jobs, the opportunity of getting help from relatives or others, and the presence of diseases external to the atrioventricular system, complicates the evaluation of the factor with which the interviews were concerned namely the effect of pacing

Good results concerning rehabilitation of the paced patients have been reported by a *number of authors*[7 41 80 111 134 225]

In an analysis of 97 paced patients, Becker Zucker Parsonnet & Gilbert[7] divided the living patients into totally satisfactorily and unsatisfactorily rehabilitated. To the totally rehabilitated group these authors assigned *those returning to work if a housewife* she should be able to discharge her household duties as well as before the onset of the illness and for the retired, they should be able to live a normal healthy life for that age group they constituted 51 per cent. In the present series those rehabilitated to a similar extent comprised 47 per cent. The satisfactorily rehabilitated should be able to engage in mild physical activity and return to household chores such as light housework, shopping and cooking This group included those who had been partially disabled before pacemaker implantation this group comprised 44 per cent, the same figure as for the present series. Unsatisfactorily rehabilitated were those that revealed no improvement or those who regressed they constituted 5 per cent in the present interview study 9 per cent would be assigned to this group There is thus a remarkably close agreement in the degree of rehabilitation between the paced patients in Becker s and the present studies. However as there is no available detailed information on Becker s patients the comparisons must be noted with reservation

From this interview study it is evident that most of the patients felt that since pacing had been started there had been an improvement in their condition. This was due largely to the relief they felt from the absence of attacks.

The mental implications of pacing were not examined systematically From the interviews it is evident that during the early period of pacing a strikingly large number *of patients did not rely on their* pacemaker units Many had functional symptoms, usually in the form of arrhythmia elicited by apprehension. The number of functional symptoms can be estimated roughly from the fact that about one third of the patients in*terviewed, regularly took sedatives or psycho*pharmacologic agents A comparative analysis of the mental state of these patients before and after pacing would probably provide new information of value in their management.

There was an improvement in the physical capacity measured in terms of the distance the patient could walk and the number of flights of stairs that could be climbed

Although some of the patients were granted disablement pensions most of them were able to resume their employement or in the case of the women, were able to manage their housework. Heavy work could be performed by patients with a fixed-rate generator running at 70 impulses/minute This is in agreement with the results of determinations of cardiac output[4, 8, 18] and of studies of the peripheral circulation[59] and with clinical observations[131] in patients using pacemakers having rates of this order This increase in physical capacity is probably not only a measure of the elevated cardiac output due to pacing[4, 18] but can to some extent also reflect reduction in the apprehension of physical activity and the effects of t

Out of a total of 204 patients with CHB but without a pacemaker Johansson[100] questioned 55 still alive at follow-up Nine had changed their occupation, while 23 had not. The rest of the patients had already retired by the onset of CHB A change of occupation was more common in his series than in the present one. Between Johansson's and the present series there may have ben differences in, for example, the attitude of the attending physician and the availability of jobs, as well as genuine differences in physical capacity

Paced patients have undergone prostatectomy[41, 66] cholecystectomy and gastrectomy[7, 111, 227] without complications, and likewise deliveries[33, 194] In the present series, too, surgical operations unrelated to the pacemaker systems and delivery were performed without complications.

In spite of the problem of hygiene, about one half of the patients of the series who were using external impulse generators preferred this type to the implanted one, mainly because a change of generator entailed no surgical operation. Most of the patients had decided opinions, in some cases after complications with implanted generators soon after acquiring a pacemaker system. A water tight external generator was first designed in October 1968 Another disadvantage of the external generator is that the site where the wires pass through the skin must be protected with sterile dressing, which requires regular changing In at least 4 cases, one of the wires was cut by mistake during this process — on one occasion with protracted attacks of arrhythmic syncope as a result

More than one third of the interviewed patients were in possession of a driving licence and about one half of these drove a car It is remarkable that only 3 had their driving licence withdrawn before pacing was begun Two of them recovered their licences and 2 received certificates of health so as to obtain a licence while using a pacemaker There is no recommendation by the National Board of Health and Welfare in the case of an application for a driving licence for a person with a pacemaker In the case of the above-mentioned 2 patients the Board supported the application with the proviso that the patient should be under continuous medical treatment and present a health certificate every year showing that there had been no change in the patient's condition that rendered him or her unsuitable to drive a motor vehicle. Both these cases may perhaps be seen as prejudicial.

As will have been seen, there are several factors that are relevant to the question of the possession of a driving licence, such as the indications for pacing, the ECG during pacing, arrhythmic syncope during pacing, complications, and mode of death. In the case of patients that had had sinus bradycardia for a long period without arrhythmic syncope and who had acquired the pace

maker to improve their physical capacity or had had intermittent conduction defects, the risk of fainting on sudden interruption of stimulation is extremely small. The same is probably true of the patients that recovered normal atrioventricular conduction but where, for safety it was considered unwise to terminate pacing. Such a high figure as 23 per cent for syncope suspectedly due to arrhythmia during pacing (p 51) a percentage of dislodgement of 29 (p 38) and a frequency of 8 per cent for threshold rises that prompted change om unit (p 38) indicate a not inconsiderable risk of arrhythmic syncope during driving for at least some of the patients of the series Even though few of the mentioned fatal outcomes were due to sudden generator failures, the percentage of sudden deaths in the whole series is high, at 15 per cent (p 67) To assess, on a general basis the risk of arrhythmic syncope during pacing is hardly possible in view of the highly varied indications for pacing Even with an improvement in the impulse generators it would probably be impossible to eliminate the risk of arrhythmic syncope or sudden death during pacing, as this sometimes occurred where there was no demonstrable generator failure An individual assessment of the circumstances relating to the possession of a driving licence by paced persons is probably desirable.

XIV THE EFFECT OF LANATOSIDE C ON VENTRICULAR AUTOMATICITY IN MAN[1]

by

O. Edhag & A. Rosén

In a routine exchange of pacemaker generators in a patient with complete heart block there is a short period during which there is no artificial stimulation; after a varying delay the idioventricular rhythm is then restored. The higher the stimulation rate the longer the period of ventricular standstill before idioventricular activity is resumed[43]. From our observations we have gained the impression that the delay in resumption of the idioventricular activity is longer in patients using digitalis. This clinical observation prompted the present experimental study of the effect of lanatoside C on the automatic ventricular activity. The study of the effect of cardiac glycosides on ventricular automaticity in laboratory animals presents difficulty of interpretation[144, 153, 213]; two preliminary studies in man point to a depressive action of this type of drug[28, 66].

MATERIAL

The study was performed on 6 paced patients with acquired complete heart block who were using an externally worn impulse generator with a switch-selected variable stimulation rate (EM 138, Elema-Schonander, Stockholm, Sweden).

In 4 patients with sinus activity the complete heart block had been diagnosed on the basis of a complete dissociation of P waves from QRS complexes, a slow ventricular rate (<40 beats/min) and broad QRS complexes (QRS<0.12 s). Two of the patients had atrial fibrillation, constant slow ventricular rates and QRS complexes longer than 0.12 s.

The ventricular complexes appearing during the interruptions in pacing usually constituted a regular rhythm, and in any one patient this pattern was identical with that recorded earlier; ventricular beats of this kind are referred to below as "regular idioventricular beats". A different kind of isolated broad ventricular complexes of variable configuration was sometimes observed; these are referred to as "isolated idioventricular beats".

Clinical data relating to these 6 patients are presented in table 42. Five of the patients had no clinical signs of heart failure at the time of the study, while one of them (no. 2) had moderate oedema and dyspnoea at rest. The heart volumes of all the patients, as calculated from radiographs exposed in the prone position[106, 142, 180], were above the normal range. The serum potassium levels determined in 4 of the patients were normal.

PROCEDURE

The experiments were carried out with the patient in the supine position. Four electrocardiographic leads (I, II, III and CR_2) were recorded continuously. A polythene catheter was inserted percutaneously into a cubital vein. The pacing at about 70 im-

[1] This study has been published in Scand. J. Clin. Lab. Invest.

TABLE 42. Anthr pometri and lini al data

Patient no.	Age	Sex	Body surface area (m²)	Heart volume (ml)	Serum potassium (mEq/l)	Duration of pacing (months)	Probable cause of the A V block	Daily medical treatment
1	62	♂	1.71	1280	4.8	2.5	Rheumatic carditis	None
2	76	♂	1.64	1200	4.1	0.5	Coronary heart disease	Hydrochlorothiazide 12.5 mg Theophyllamine 0.2 g
3	79	♂	1.77	920	4.4	46.0	Coronary heart disease	Furosemide 20 mg Cloxacillin 2 g
4	77	♀	1.85	960		18.0	Myocarditis	Hydrochlorothiazide 25 mg Potassium chloride 0.5 g
5	83	♀	1.56	760	4.8	4.0	Syphilitic aortitis	Furosemide 40 mg
6	72	♂	1.92	1130		9.0	Rheumatic heart disease	Adelphin-Esidrex (Ciba) 1 tablet

pulses/min was interrupted abruptly — 3 times in 5 patients and twice in one patient — at intervals of 10 minutes. The ventricular standstill lasted from 1.5 to 9 s. If the patient experienced any kind of discomfort during a break, pacing was immediately restarted (When, in one patient [no 1] the idioventricular rhythm was not established after interruption at a stimulation rate of 70 impulses/min this was reduced to about 50 per minute.) The patients were familiar with this procedure from earlier routine examinations of their pacemaker units on the occasions when the generator was being changed and the stimulation threshold determined

At this stage 1.2 mg of lanatoside C (Cedilanid Sandoz) was administrered as a 5 minute intravenous infusion. Thirty minutes later the pacing was interrupted again and the above procedure repeated.

Three of the patients (nos. 4—6) were subsequently given 250 mg of digoxin a day by mouth and re-examined by the same process of interruption of the pacing after 90 3 and 54 days, respectively

RESULTS

Before the administration of lanatoside C, *regular idioventricular beats* were registered within 5 s of discontinuing stimulation in all but one of 17 trials (Fig 17) after infusion of the drug the figure was only 2 out of 17 interruptions the difference is statistically significant ($P<0.001$)

Regular or isolated idioventricular beats were registered during the first 5 s in all but one of 17 trials before, and in 5 out of 17 trials after administration of lanatoside C (Fig 17) the difference is statistically significant ($P<0.01$)

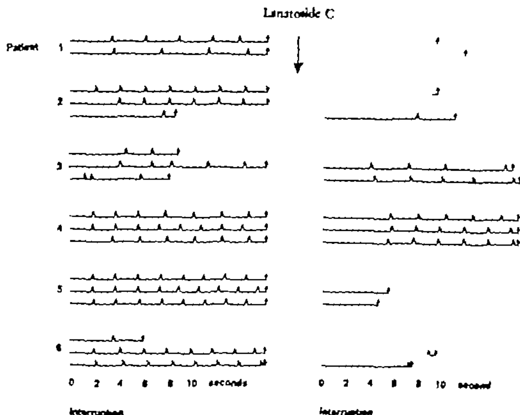


Figure 17 The occurrence of regular ( ) and isolated (▲) ventricular beats after interruption of pacing before and after intravenous administration of lanatoside C (1.2 mg)

The *mean duration of ventricular standstill* after the interruption of the pacing was 3.0 (±0.36) s before administration of the drug against 5.7 (±0.44) s afterwards the difference is statistically significant ($P<0.001$). In 3 patients (nos 1, 5 and 6) the pacing was resumed because of the occurrence of symptoms before any regular idioventricular activity had appeared.

The 3 patients in whom a further examination was made during continuous oral administration of digoxin likewise showed a delayed resumption of idioventricular activity on interruption of pacing. In these patients (nos. 4—6) the duration of the ventricular standstill was 4.5, 3.6 and 7.6 s. The corresponding figures in the experimental study after administration of lanatoside C were 6.6, 4.9 and 7.9 s.

The mean atrial rate during the first 5 s of the interruptions was the same as before the infusion of lanatoside C.

One hour after the drug had been given one patient (no. 5) complained of nausea, which lasted a couple of hours; the other patients did not report any discomfort.

DISCUSSION

The delay in resumption of idioventricular activity following a break in pacemaker stimulation reflects the degree of automat

— There was a large variation in the number of attacks of arrhythmic syncope before pacing was begun. On average 21.8 months elapsed between the first attack and the introduction of pacing. One quarter of the patients suffered external head injuries or extremity fractures during attacks. Attacks of arrhythmic syncope constituted the most common indication for pacing; however some 10 per cent of the patients had had none. Severe or moderate heart failure accompanied by a reduced physical capacity were the most common contributory grounds for introducing pacing. While using a pacemaker 23 per cent of the series had attacks of arrhythmic syncope. In about one half of these the pacemaker system was found to be defective. None of the patients suffered any injury during these attacks. Cerebral confusion in some of the patients before pacing had been introduced, subsequently disappeared in all but one case.

Severe heart failure was a fairly common finding at the follow-up examination. A feeling of arrhythmia was experienced by 44 per cent of the patients during pacing. Twitching of the abdominal muscles near the indifferent electrode was common, especially just after pacing had started. The heart volume at radiologic examination during the first months of pacing was not significantly smaller than during the last months before pacing in the case of patients radiographed within these intervals.

ECGs before and during pacing — For a long time before pacing was begun many of the patients had had conduction defects, and a number also complete heart block. In about 10 per cent of the series no complete heart block had been recorded before the introduction of pacing. These had instead A V block II, sinus bradycardia, sinus rhythm or atrial fibrillation with numerous ventricular ectopic beats and slow-rate atrial fibrillation. In 77 per cent the ECGs registered just before the pacemaker was provided disclosed complete heart block.

During the pacing with fixed rate generators about one half of the series had paced rhythm without competition or ventricular ectopic beats. Of the 72 per cent of the patients where an ECG was registered during a short break in stimulation one half recovered atrioventricular conduction. Out of 83 patients in whom only complete heart block had been recorded before provision of the pacemaker 46 subsequently had regular paced rhythm. A close agreement was found between recorded ventricular ectopic beats before and during the pacing, as well as during a short interruption in pacing.

Survival — The one-year survival of 86 per cent for the series was much higher than for unpaced patients with complete heart block. During an observation period of up to 6 years of pacing the survival rate remained high.

Mode of death and autopsy findings — Sudden death was the commonest mode of decease, occurring in 38 out of the 62 patients with a fatal outcome. Most of these had faulty pacemaker units or had recently suffered myocardial infarction: evidence of this condition was found in 23 of the 52 patients on whom an autopsy examination was performed; in 17 of them an infarct less than 2 weeks old was found. With one exception infarction was unaccompanied by chest pains. Pacemaker defects and aortic valvular heart disease were common among the young men with a fatal outcome. Here, heart failure was more severe than in the other men comprising the deceased group.

Clinical findings among the deceased — Before introduction of pacing angina pectoris, heart failure, ventricular ectopic beats

and atrial fibrillation or flutter were commoner among the patients dying during pacing than among those still living at the end of the observation period. Ventricular ectopic beats were also more common during pacing in the deceased group and in the patients with histologically confirmed myocardial infarction than in the rest of the deceased Arrhythmic syncope during pacing was more common among those that had died than those still living at the end of the observation period. Use of digitalis was also more frequent in the deceased group than in the rest of the series.

Rehabilitation of the paced patient — At an interview study of 139 consecutive paced patients performed in collaboration with a welfare officer 73 per cent of those questioned felt there had been an improvement The patients did not feel that the pacing appreciably interfered with the pursuit of their occupation Even physically heavy work could be performed. Nonetheless, a fairly large proportion of the patients had been granted a disability pension The physical capacity was better during than before pacing, as measured by the distance walked on level ground and the number of flights of stairs that could be managed without respiratory distress Of the patients with externally worn impulse generators about one half reported hygiene problems In spite of this there were many that had no wish to change over to an implanted generator On the basis of this case series, the use of a pacemaker is not incompatible with possession of a driving licence

The effect of lanatoside C on ventricular automaticity in man — The effect of lanatoside C on the ventricular automaticity was examined in 6 pacemaker patients with complete heart block. On interrupting the pacing there was a mean period of ventricular standstill of 3 0 s before ventricular activity was re-established. After intravenous administration of 1.2 mg of lanatoside C followed by repeated interruptions of pacing, the duration of ventricular standstill was significantly increased. A suppressive action of this drug on the ventricular automaticity might conceivably be produced indirectly through inhibition of the increase in cardiac sympathetic inflow but this would seem improbable in view of the fact that the sinus rate was not altered by administration of the agent. A more likely alternative is that lanatoside C exerts a direct depressive effect on the ventricular automaticity

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By Olof Selroos

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To My Famil

FROM THE MJÖLBOLSTA HOSPITAL AND THE FOURTH DEPARTMENT OF MEDICINE,
HELSINKI UNIVERSITY CENTRAL HOSPITAL, FINLAND

THE FREQUENCY, CLINICAL PICTURE AND PROGNOSIS OF PULMONARY SARCOIDOSIS IN FINLAND

BY

OLOF SELROOS

HELSINKI–HELSINGFORS 1969

Translated by Eva Palmgren

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CONTENTS

I INTRODUCTION

Sarcoidosis is a disease which may involve most organs. The manifestations which first attracted attention were cutaneous. A condition described by Besnier (1889) under the name lupus pernio is the first instance reported of indubitable sarcoidosis of the skin. Besnier's patient was a 34-year-old man in whom lesions of the nose, ears and fingers had been present for ten years. The nose was enlarged, livid purplish-red, with a shining surface and dilated pores. There were also erosions at the nostrils. The sensibility and temperature of the skin were normal. Many fingers were purplish-red and swollen, and some nails were affected. Besnier's description of lupus pernio of the nose is characteristic and still valid.

Besnier did not investigate the lesions histologically. The first to publish a histological description of a similar case was Tenneson (1892), who drew attention to the abundant occurrence of epithelioid cells and the scantiness of giant cells. The histological picture resembled that of lupus, but a lupus with special histological features described as myxomatous and oedematous.

Hutchinson (1898) published a report on »Mortimer's malady». He described four cases. The most typical — »the first and as yet the most marked example» — was that of a 65-year-old woman whose name was Mortimer. Her cheeks and upper extremities exhibited patches which were symmetrically located, though of different sizes. These lesions were slightly elevated, soft, well-defined and dark red. The right external ear was affected and the nose showed tumorous swelling, though no cutaneous changes. Hutchinson concluded that the disease involved was very likely either tuberculous in nature or a form of lupus, though obviously differing from those previously known. He therefore suggested the name »lupus vulgaris multiplex non-ulcerans et non-serpiginosus». Although no histological investigation was performed, it may safely be assumed that Mortimer's malady was the same disease as the »multiple sarcoid» described by Boeck one year later.

Most surveys state that the first case of sarcoidosis was described by Hutchinson as early as 1877 in a report called »Case of livid papillary psoriasis». However, Scadding (1967), who thoroughly studied this question, is convinced that Hutchinson himself never regarded this case as identical with Mortimer's malady and concluded that »the grounds for making this identification retrospectively seem rather tenuous.»

Boeck (1899) described in detail the case of a 36-year-old policeman with multiple skin manifestations. He found that the lesions resembled those described by Hutchinson. In addition, Boeck's patient showed very large epitrochlear lymph nodes, less enlarged axillary nodes and somewhat enlarged cervical and inguinal nodes. On histological investigation of two subcutaneous nodules Boeck found »sharply circumscribed foci of a new growth» in which the cells consisted of »epithelioid connective-tissue cells». He also observed giant cells of »sarcomatous type». The lesions were mostly perivascularly located. Boeck suggested the name multiple benign sarcoid of the skin, because the changes »might be described as perivascular sarcomatoid tissue built up by excessively rapid proliferation of epithelioid connective-tissue cells in the perivascular lymph spaces». Boeck also described another similar case. He was the first to notice generalized lymph node enlargement in connection with sarcoidosis, and also gave the first detailed histological description of the lesions. Later Boeck changed his opinion concerning the nature of the disease. When he had detected acid-fast bacilli in the nasal mucosa of a patient, he concluded that the disease was infectious and closely related to tuberculosis. He then suggested the name benign miliary lupoid (1905). In a later paper Boeck (1916) emphasized

the resemblance between this disease and the lupus pernio described by Besnier. He also described chronic pulmonary lesions and changes of the bone and conjunctiva.

Kreibich (1904) was the first to notice cyst-like skeletal changes associated with lupus pernio. Rieder (1910) described similar changes under the name of chronic osteomyelitis. In 1920 Jüngling published a report on two cases of what he called »ostitis tuberculosa multiplex cystica» and in a later study (1928) he described the histology of the bone lesions in question and discussed the close association between the skeletal changes and lupus pernio and benign miliary lupoid.

Schaumann (1914–1918) established that lupus pernio and benign miliary lupoid were manifestations of the same skin disease, which sometimes also involved the lymph nodes, tonsils, nasal mucosa, lungs and bone. He also showed that the lesions were histologically uniform and consisted of tuberculoid granulomas, which were markedly proliferative and showed no signs of exudation. Since the changes were most frequently encountered in lymphatic tissue, he suggested that the disease be called lymphogranulomatosis benigna. Schaumann also pointed out that the skin lesions should not be considered the principal feature: they are only one sign of the disease and skin manifestation is not necessarily present. He finished his extensive studies on benign lymphogranulomatosis with a survey (1936), in which he stated that the disease is generalized and probably of tuberculous etiology.

Heerfordt (1909) described the »febris uveoparotidea» syndrome, which he regarded primarily as a chronic form of mumps, but later when he had succeeded in demonstrating a tuberculoid tissue reaction, considered as a form of tuberculosis. In the 1930's Bruins Slot (1936) and Pautrier (1937) established that the syndrome is a form of sarcoidosis, a view that has been generally accepted. Febris uveo-parotidea is a relatively rare manifestation of sarcoidosis. On the other hand, ocular symptoms alone (uveitis, iridocyclitis and conjunctival symptoms) are relatively common (James 1959a).

Today it is quite clear that most organs can be affected in sarcoidosis. The organs most frequently involved are the lymph nodes, lungs, liver, spleen, skin, eyes, the small bones of the hands and feet and the salivary glands. Almost all organs have at some time been mentioned in occasional case reports.

The occurrence of bilateral enlargement of the hilar lymph nodes in sarcoidosis was noticed by Schaumann as early as 1914. This observation was later verified by many other authors (Kuznitzky and Bittorf 1915, Martenstein 19 4, Burger and Küthe 1939, Ustvedt 1949). It was mainly Löfgren (1946, 1952 a and b, 1953 a), however, who recognized that bilateral symmetrical hilar node hyperplasia is an early form of sarcoidosis, which often develops in association with erythema nodosum. Löfgren (1953 b) was also able to show that in this form of sarcoidosis the prognosis is markedly better than in chronic cases with involvement of many organs.

When the clinical features of sarcoidosis had been clarified, epidemiological research began in many parts of the world. Sarcoidosis seems to be more common in the temperate and subarctic zones than in the equatorial regions (Chapman 1955). In the U.S.A. the disease is much more prevalent among negroes than among whites (Ricker and Clark 1949, Longcope and Freiman 1952, Israel and Sones 1958, Mayock et al. 1963), while only a few Indian and Chinese cases have been observed (Present and Siltzbach 1967). High prevalence rates have been reported from the Scandinavian countries, where numerous symptom-free patients with bilateral hilar node hyperplasia have been detected by routine chest radiography (Wallgren 1958). Many investigators have noted higher rates in women than in men (Reisner 1944, Longcope and Freiman 1952, Löfgren 1953 a, Mayock et al. 1963), and a relationship between pregnancy and the onset of illness has been observed (Löfgren and Lundbäck 195? a, Franz and Wurm 1962, Fried 1964).

Etiology. The patho-anatomical picture of sarcoidosis is identical with that of productive tuberculosis (Zettergren 1954, Teir et al. 1962, Määttä 1968). It is therefore understandable that the early investigators regarded sarcoidosis as a form of tuberculosis (Tenneson 1892, Boeck 1905, Jüngling 1920). Moreover, instances of a transition from sarcoidosis to tuberculosis have been reported (Riley 1950), and in some cases clinical tuberculosis has been followed by sarcoidosis (Hiatt 1948, Scadding 1960). Patients showing both diseases concomitantly have also been described (Scadding 1967). The relationship between sarcoidosis and tuberculosis was thoroughly studied by Wurm (Wurm et al. 1963, 1965). The transitional forms and the concurrence of the two diseases were considered as evidence in favour of a tuberculous etiology. Scadding (1967) mentioned nine important points supporting the view that sarcoidosis is a form of tuberculosis and eight points arguing against this theory. He ventured the tentative conclusion that in England, at least, most cases of sarcoidosis seemed to be tuberculous in origin.

Many other hypotheses have also been advanced. Without entering on a discussion of them, some of the most important theories may be mentioned. It has been suggested that sarcoidosis is caused by a specific, though as yet unidentified infective agent.

The possibility of both viral (Löfgren and Lundbäck 1950) and fungal infection (Törnell 1946) has been discussed. Specific, non-infectious factors, in particular pine pollen, have attracted great interest (Cummings and Hudgins 1958). The theory has been advanced that sarcoidosis is a collagen disease of the same type as polyarteritis nodosa (Jackson and Kass 1953 Kass et al. 1953 Tellum 1964) Teilum (1948) had previously suggested that an allergic hyperglobulinosis in the reticuloendothelial system might be involved, due to repeated stimulation of certain immune mechanisms. Histochemical investigations have also revealed changes resembling those seen in collagen disease (Wanstrup and Elling 1968) The hypothesis of a »terrain sarcoïdique» has found many advocates (Darrier 1934) According to this, certain individuals have a tendency to react to a great number of different stimuli by granuloma formation. It has been convincingly shown, however that this explanation does not hold good. (Refvem 1954 Hurley and Shelley 1959).

During the last few years a variety of deviations in the reactive pattern of patients with sarcoidosis have been revealed. It has therefore been suggested that sarcoidosis is »dependent upon an immunologically determined alteration of reactivity of a peculiar sort, to which certain individuals may be especially prone· and that in individuals liable to this type of altered reactivity sarcoidosis occurs in response to certain specific agents, possibly including that responsible for the altered reactivity» (Scadding 1967).

Some reports from the last decade have brought up evidence in favour of an association between sarcoidosis and »anonymous» mycobacteria (Runyon Type I) (Chapman 1961 Chapman and Speight 1964 1967 Chapman et al. 1967). Very interesting studies have also been published on the association between sarcoidosis, mycobacteria and mycobacteriophages (Mankiewicz and van Walbeck 1962, Mankiewicz 1963 1964 1966, 1967).

In spite of extensive research the etiology of sarcoidosis is still an unsolved problem.

Definition. It is difficult, not to say impossible, to define a disease of obscure etiology All definitions offered are therefore descriptive in character The first descriptive definition was formulated in 1948 by a subcommittee of the National Research Council and modified by a second committee in 1956. In connection with the Second International Conference on Sarcoidosis in Washington D C., 1960 a new descriptive definition was suggested by the medical group: »Sarcoidosis is a systemic granulomatous disease of undetermined etiology and pathogenesis. Mediastinal and peripheral lymph nodes, lungs, liver spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected. The Kveim reaction is frequently positive and tuberculin-type hypersensitivities are frequently depressed. Other important laboratory findings are hypercalciuria and increased serum globulins. The characteristic histologic appearance of epithelioid tubercles with little or no necrosis is not pathognomonic, and tuberculosis, fungal infections, beryllium disease, and local sarcoid reactions must be excluded. The diagnosis should be regarded as established for clinical purposes in patients who have consistent clinical features, together with biopsy evidence of epithelioid tubercles or a positive Kveim test.»

Later international conferences on sarcoidosis were held in Stockholm in 1963 and in Paris in 1966 but no additions to this definition were considered necessary Sarcoidosis was also discussed at a conference on tuberculosis in Düsseldorf in 1964 and at a dermatological conference at Freiburg im Breisgau in 1965

The literature concerning sarcoidosis is copious In 1964 the National Library of Medicine, U S. Department of Health, Education and Welfare published a bibliography comprising 3,592 references (Mandel et al. 1964). Since then, over 100 papers have been added to the list annually Within the scope of the present paper it is therefore impossible to discuss anything but the most important contributions. Extensive surveys have been published e.g. by Hunter (1936), Longcope and Pierson (1937), Freiman (1948) Ricker and Clark (1949), Leitner (1950), Longcope and Freiman (1952), Cowdell (1954), Middleton (1954) Israel and Sones (1958), Smellie and Hoyle (1960), Siltzbach (1961a), Scadding (1961 1967), Cummings and Hammarsten (1962), Mayock et al. (1963), Lebacque (1964) and Atwood and Nelson (1965). The radiology of the lungs has been treated e.g. by Nitter (1953) and Wurm et al. (1958)

II. PURPOSE OF THE STUDY

The papers on sarcoidosis published in Finland are few. No extensive epidemiological investigation has been performed. The clinical picture has been described only on the basis of selected patient groups and the series have been small. The prognosis of sarcoidosis has been discussed by the present writer in a preliminary study on early sarcoidosis.

Reports from various parts of the world have shown that the frequency, clinical picture and prognosis of sarcoidosis are different in different countries, races, sexes and age groups.

The purpose of the present study was

1) to estimate the frequency of pulmonary sarcoidosis in Finland on the basis of mass radiographic surveys and hospital series,
2) to describe the clinical picture of pulmonary sarcoidosis as it appears in Finland, and
3) to analyse the development and prognosis of pulmonary sarcoidosis in different patient groups.

III. THE FREQUENCY OF PULMONARY SARCOIDOSIS IN FINLAND

INTRODUCTION

The frequency and distribution of a disease in a defined geographical area can be estimated only if the cases are reliably diagnosed and recorded. For diseases of major public interest such as certain contagious diseases (e.g. tuberculosis) and malignant tumours, central registers have been instituted and notification is compulsory. It is thus possible to run statistics which are continuously up to date as regards new cases, cured cases, chronic cases, recurrences, deaths, etc. In respect to sarcoidosis, it appears that notification has been introduced as a regular procedure only in Denmark (Horwitz 1964).

The majority of studies on the frequency of sarcoidosis have been based on clinical hospital series. It goes without saying that estimates of this type are open to error of many kinds and can only give an approximate idea of the true prevalence of the disease. The different series are not comparable, either since interest in the disease and diagnostic facilities have varied.

Comparable studies on the prevalence of sarcoidosis in different areas have been facilitated by the introduction of mass chest radiography. Although the detection of pulmonary tuberculosis is the main purpose of mass radiographic surveys, other diseases of the lung may be revealed at the same time. Since practically all sarcoidosis patients show intrathoracic changes, the data thus collected have also proved valuable in estimating the prevalence of sarcoidosis. As regards the results it is necessary however to consider the extent to which suspected cases have been verified and to ask whether the population investigated was selected or truly representative of the community.

In Finland, the frequency of sarcoidosis has previously been studied in a limited area in the south (Selroos 1967). A clinical series consisting of all sarcoidosis patients admitted to Finnish hospitals in 1960 has been analysed (Riska and Selroos 1964). A preliminary report on the prevalence of sarcoidosis in mass radiography material has been published (Pätiälä et al. 1964), but this was based in part on suspected findings which were not clinically verified.

In order to estimate the frequency of sarcoidosis in Finland 12 areas were chosen for study. Within these, investigations were carried out for six years, taking into account both mass radiography data (prevalence study) and the total number of new cases detected annually irrespective of the mode of detection (incidence study). In addition, all sarcoidosis patients admitted to Finnish hospitals in 1967 were scanned in order to analyse the development between 1960 and 1967.

MATERIAL AND RESULTS

Prevalence of sarcoidosis

In Finland, compulsory mass radiographic surveys for tuberculosis are as a rule carried out in the various tuberculosis districts once every three years. In the 1950's sarcoidosis was still unknown to many Finnish physicians, and the disease was not confidently diagnosed until the 1960's. For these reasons the two three-year periods 1962–1964 and 1965–1967 were chosen for study. The regions studied appear on the map in Fig. 1. They were chosen so as to differ as much as possible in regard to the tuberculosis situation. This was estimated on the basis of the following facts. Until Dec. 31 1965 no consistent principles were applied to the registration of tuberculosis in Finland. There was, for instance, no agreement as to the criteria for keeping patients on record. Since Jan. 1 1966, a uniform and simple system of registration has been applied, on the basis of which more reliable data are available. Hence, only data relating to 1966 and 1967 have been considered. The parameters used were 1) the number of new bacteriologically verified cases of pulmonary tuber

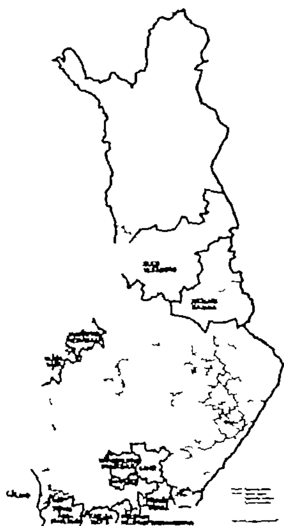


Fig. 1 Tuberculosis dispensary districts in which sarcoidosis prevalence and incidence studies were performed in 1962–1967

Ranking list of Finnish tuberculosis dispensary districts, calculated on tuberculosis figures for the years 1966 and 1967. The districts chosen for study are indicated by *italics*

	Final ranking points	Dispensary district	Tuberculosi district
1	2.	Kauhajoki	Härmä
2.	*29.5*	*Riihimäki*	Kanta-Häme
3	30	Rovaniemi	Lappi
4	*35*	*Oulu/Uleåborg*	Pohjois-Pohjanmaa
5	40	Lapua	Härmä
6.	46	Oulainen	Keski-Pohjanmaa
7	48	Turku	Varsinais-Suomi
8	54	Seinäjoki	Härmä
9	56	Kemi	Lappi
10.	61	Iisalmi	Pohjois-Savo
11	61.5	Helsinki/Helsingfors	Helsinki/Helsingfors
12.	65.5	Kokkola	Härmä
13	*67*	*Mikkeli*	Kymi-Mikkeli
14	*71.5*	*Hämeenlinna/ Tavastehus*	Kanta-Häme
15	*76*	*Vasa/Vaasa*	Vasa
16.	77	Rauma	Satakunta
17	81	Forssa	Kanta-Häme
18	84.5	Kemijärvi	Lappi
19	85	Thuruniemi	Kymi-Mikkeli
20	*85*	*Kajaani/Kajana*	Pohjois-Pohjanmaa
21	85.5	Tampere	Keski-Häme
22	*95*	*Lahti/Lahtis*	Kanta-Häme
[illegible]3	95	Kuopio II	Pohjois-Savo
24.	96.5	Vammala	Satakunta
25.	*97*	*Borgå, Porvoo*	Raseborg
26.	99	Helsinki	Uusimaa
27	*100.5*	*Joensuu*	Pohjois-Karjala
28.	101	Kristinestad	Vasa
29	105.5	Saarijärvi	Keski-Suomi
30.	105.5	Salo	Varsinais-Suomi
31	106	Jyväskylä	Keski-Suomi
3[illegible]	107.5	Kankaanpää	Satakunta
33	111.5	Kuopio I	Pohjois-Savo
34	11[illegible].5	Lappeenranta	Kymi-Mikkeli
35	114.5	Nurmes	Pohjois-Karjala
36.	123.5	Pori	Satakunta
37	128	Savonlinna	Kymi-Mikkeli
38.	136	Kotka	Kymi-Mikkeli
39	139.5	Kuusankoski	Kymi-Mikkeli
40	*139.5*	*Helsingfors/Helsinki*	Raseborg
41	*139.5*	*Jakobstad/Pietarsaari*	Vasa
42.	154	Turun ympäristö	Varsinais-Suomi
43	*155.5*	*Åland*	Åland
44	*156.5*	*Karis/Karjaa*	Raseborg
45.	*163.5*	*Åbo/Turku*	Raseborg
46.	166	Varkaus	Pohjois-Savo

culosis, 2) the number of pulmonary cases listed in the tuberculosis register 3) the number of chronic cases of pulmonary tuberculosis and 4) the number of deaths from tuberculosis. Each parameter was calculated on the whole population of the tuberculosis districts. Then the tuberculosis dispensary districts were ranked for each particular parameter to give ranking figures. By summing up the figures for the two years considered, a final ranking list was made for each parameter. The ranking figures for the four different parameters were summed up. Thus, a final ranking list for the various dispensary districts was obtained, which reflects the situation in regard to tuberculosis. The areas shown on the map were chosen on this basis. The dispensary districts of Oulu and *Riihimäki* represent regions with an unfavourable tuberculosis trend, while Åland and the Karis and Åbo dispensary districts in the tuberculosis district of Raseborg were chosen as areas with a favourable trend. This is in agreement with familiar data on the epidemiology of tuberculosis in Finland. The remaining dispensary

districts represent an intermediate group for which no sharp distinctions can be made.

The mass radiographs were read by two physicians, one representing the firm which performs the radiophotography and one representing the tuberculosis dispensary. Pathological findings were recorded and measures taken for more exact diagnosis. On the basis of these primary findings all patients with suspected sarcoidosis were followed up by the writer. The present study includs only cases in which the diagnosis of sarcoidosis was confirmed and other diseases were ruled out. The final diagnosis was based on the results of examination in a hospital or sanatorium.

Table I shows the mass chest radiography data. In the dispensary districts studied the prevalence of sarcoidosis ranged from 2.3 to 16.7 per 100,000 examined during the period 1962–1967. The prevalence in the whole material of 1,530,178 radiographs was 7.5 per 100,000. No correlation with the situation in regard to tuberculosis was observed. Low rates for sarcoidosis were noted both in districts with an unfavourable tuberculosis trend (Oulu 3.8 per 100 000) and in districts with a favourable trend

Table I. Prevalence of verified pulmonary sarcoidosis in mass radiographic surveys in 1962–1967

Year	Dispensary districts in the Tuberculosis district of Pohjois-Pohjanmaa						Dispensary districts in the Tuberculosis district of Vasa					
	Oulu/Uleåborg			Kajaani/Kajana			Vaasa/Vasa			Pietarsaari/Jakobstad		
	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000
1962	0	67 610	0	0	17 433	0	0	24 465	0	5	39,929	12.5
1963	1	23 156	4.3	1	21,357	4.7	3	31 644	9.5	0	17 153	0
1964	3	39 060	7 7	1	25 498	3.9	1	31 601	3.[illegible]	5	32,458	15 4
1965	7	70 737	9.9	0	[illegible]3,573	0	0	22,720	0	0	19,607	0
1966	0	39,566	0	1	27 193	3 7	4	17,940	22.[illegible]	5	29 144	17.2
1967	0	50,715	0	1	28 181	3.5	3	39,064	7 7	0	28,531	0
1962–1967	11	290,844	3.8	4	143,235	2.8	11	167 474	6.6	15	166,822	9 0

Year	Dispensary districts in the Tuberculosis district of Kanta-Häme									Tuberculosis district of Åland		
	Riihimäki			Hämeenlinna/Tavastehus			Lahti/Lahtis					
	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000
1962	1	6,395	15 6	0	26,227	0	0	23,943	0	1	12,49	8.0
1963	1	5,337	18 7	0	20,178	0	3	64 494	4 7	0	73	0
1964	0	13 127	0		8,733	22.9	1	11,257	8.9	0	6,786	0
1965	1	18 401	5 4	4	23,368	17 1	3	19,295	15.5	0	6,291	0
1966	1	5,975	16.7	2	20,833	9 6	1	44 710	2.2	0	6,910	0
1967	3	15 004	20.0	5	12,503	40 0	7	43 738	16.0	0	6,149	0
1962 1967	7	64,239	10.9	13	111,842	11 6	15	207 437	7.2	1	38 701	2.3

Year	Dispensary districts in the Tuberculosis district of Raseborg											
	Helsinki/Helsingfors			Porvoo/Borgå			Karjaa/Karis			Turku/Åbo		
	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000	No. of pat.	No. of radiographs	Prevalence per 100,000
1962	3	18,655	16.1	0	24 189	0	0	13 155	0	0	8 654	0
1963	3	19,014	15 8	0	10,597	0		13,544	14 7	0	7,553	0
1964	2	13 425	15.0	1	14 067	7 1	1	11,38	8.8	1	6,946	14 4
1965	3	18,987	15.8	5	19 470	25 7	1	13,303	7.5	3	6,978	43.0
1966	4	19,521	20.5	2	17 646	11.3	2	13,589	14 7	1	7 476	13 4
1967	3	18 490	16 2	3	20,851	14 4	1	13 706	7.3	0	8 366	0
196 1967	18	108,092	16 7	11	106 820	10.3	7	78,699	8.9	5	45,973	10.9

(Åland 2.3 per 100,000). Similarly a high prevalence of sarcoidosis was found to be connected with both an unfavourable and a favourable tuberculosis trend (Riihimäki, 10.9 per 100,000 and the Åbo dispensary district of the tuberculosis district of Raseborg, 10.9 per 100,000) The highest prevalence of sarcoidosis was noted in an area with an intermediate tuberculosis status (the Helsingfors dispensary district of the tuberculosis district of Raseborg, 16.7 per 100 000). As regards the various years of the period under study no clear increase or decrease in the number of new cases was observed.

Incidence of sarcoidosis

The total frequency of sarcoidosis during the period 1962—1967 in this paper called the incidence of sarcoidosis, was analysed in the same tuberculosis dispensary districts in which the prevalence study was performed. In the incidence study all new cases of sarcoidosis were considered, irrespective of the mode of detection. Data were obtained from tuber culosis dispensaries, central sanatoria, local hospitals, district hospitals, central hospitals and university central hospitals. An attempt was thus made to

Table II. Annual incidence of verified pulmonary sarcoidosis in 196.—1967

Year	Dispensary districts in the Tuberculosis district of Pohjois-Pohjanmaa						Dispensary districts in the Tuberculosis district of Vasa					
	Oulu/Uleåborg			Kajaani/Kajana			Vaasa/Vasa			Pietarsaari/Jakobstad		
	No of new cases	Mean popula tion	Incidence per 100,000	No of new cases	Mean popula tion	Incidence per 100,000	No f new cases	Mea popula-tion	Incidence per 100,000	No. of new cases	Mean popula tion	Incidence per 100,000
1962	3	194 950	1.5	0	92,879	0	1	71 118	1 4	7	69 797	10.0
1963	7	197 425	3.5		93,519	2.1	3	71,965	4.2	1	71,305	1 4
1964	8	200 137	4 0	3	94 436	3.2	3	72,975	4 1	10	72,789	13 7
1965	12	201,522	6.0	3	94 787	3.2	0	73 727	0	1	74,049	1 4
1966	12	202,510	5.9	6	94 888	6.3	8	74 053	10.8	5	75,007	6.7
1967	9	205 748	4 4	3	94,500	3.2	6	79,307	7 6	2	75 000	2.7
Mean values 196. 1967	8.5	200,349	4.2	2.8	93 689	3.0	3.5	75,212	4 7	4.3	72,398	5.9

Year	Dispensary districts in the T berculosis district of Kanta-Häme									Tuberculosis district of Åland		
	Riihimäki			Hämeenlinna/T vastehus			Lahti/Lahtis					
	No of new cases	Mean popula tion	Incidence per 100,000	No. of new cases	Mean popula-tio	Incidence per 100,000	No f new cases	Mean popula-tion	Incidence per 100,000	No. of new cases	Mean popula-tion	Incidence per 100,000
196	3	38,184	7.9	0	84,348	0	4	143,951	2.8	1	21,083	4 7
1963	3	38,259	7.8	1	83,858	1.	3	146,790	2.0	1	1 116	4 7
1964	0	38 149	0	3	84,743	3 5	5	150,362	3.3	2	21,271	9 4
1965	4	38,053	10.5	6	84,86	7 1	5	153 665	3.3	0	21,37?	0
1966	2	38 024	5.3	7	84 407	8.3	1	156,318	0.6	0	1 481	0
1967	4	38 151	10.5	6	84,954	7 1	9	159 879	5 6	1	21 087	4 7
Mea values 196.–1967	2.7	38 167	7 1	3 8	84 651	4.5	4 5	151,915	3 0	0.8	21 085	3.8

Yea	Dispensary districts in the Tuberculosis district of Raseborg											
	Helsinki/Helsingfors			Porvoo/Borgå			Karjaa/Karis			Turku/Åbo		
	No. f new cases	Mean popula-tion	Incidence per 100,000	No. of new cases	Mean popula-tion	Incidence per 100,000	No. of new cases	Mean popula tion	Incidence per 100,000	No. of new cases	Mean popula-tion	Incidence per 100 000
1962	8	75 870	10.5	2	65,984	3.0	2	4.,323	4 7	1	26,811	3 7
1963	12	80,571	14 9	1	66,088	1.5	4	42,734	9 4	1	26,485	3.8
1964	8	86 571	9	5	61,095	8 2	5	43,025	11 6	2	26,305	7 6
1965	1	92,267	13 0	10	61 751	16.2	2	43,292	4 6	5	26,132	19 1
1966	11	97,242	11 3	4	62,489	6.4	6	43,346	13.8	1	25,907	3.9
1967	13	102,605	12.7	4	63 390	6.3	2	42,402	4.7	0	25,797	0
Mea values 196. 1967	10.7	89,.37	12.0	4 3	64 687	6 6	3.5	42,362	8.3	1 7	26,304	6.5

clarify the situation as completely as possible in the areas under study during the period covered by this investigation.

The data related to the incidence of sarcoidosis are shown in Table II. The average annual incidence of new cases ranged from 3.0 per 100,000 of population (the Kajaani and Lahti dispensary districts) to 12.0 per 100,000 (the Helsingfors dispensary district of the tuberculosis district of Raseborg). The mean incidence observed in this study calculated on an average population of 960,056, was 51 new cases annually which makes 5.3 per 100,000 of population. As calculated for the whole country with a population of about 4.5 million, this would mean that approximately 240 new cases of sarcoidosis are detected every year

When the incidence of sarcoidosis was considered in relation to the tuberculosis situation as was done in the prevalence study no correlation was observed. A low incidence of sarcoidosis (3.0 to 4.5 per 100,000) was noted both in areas with a favourable tuberculosis trend (Åland, 3.8 per 100,000) and in areas with an unfavourable trend (Oulu, 4.2 per 100,000) The highest three figures were noted in areas which were quite different in regard to tuberculosis, i.e. in a district with an unfavourable trend (Riihimäki, 7 1 per 100,000), in a district of the intermediate group in this respect (the Helsingfors dispensary district of the tuberculosis district of Raseborg, 12.0 per 100 000) and in a district with a favourable tuberculosis trend (Karis, 8.3 per 100,000). Neither the results of the incidence study nor those of the prevalence study revealed any definite increase or decrease in the annual number of new cases of sarcoidosis during the six-year period studied.

Hospital cases from the whole country

In 1960 and 1967 the Statistical department of the National Board of Health ran a special diagnosis record comprising all patients discharged from Finnish hospitals and treatment centres in those years. It was thus possible to trace all sarcoidosis patients hospitalized during the years in question. The purpose of this phase of the present study was in part to find out whether the actual number of diagnosed new cases agrees with the number calculated on the basis of the incidence in the 12 areas chosen for study and in part to analyse the development from 1960 to 1967 The present writer either visited or contacted by letter those hospitals in which sarcoidosis patients had been treated and thus had access to the records for evaluation of the acceptability of the diagnosis.

In 1960, patients with sarcoidosis were treated at 3 Finnish hospitals, all of which placed their records at the writer's disposal. There were 71 definite or highly probable cases of sarcoidosis. Of these, 16 were previously diagnosed and 55 were new cases. The geographical distribution of the new cases appears in Fig . In 26 cases diagnosed as sarcoidosis, the diagnosis proved to be erroneous or could not be accepted owing to inadequacy of the investigations performed and absence of convincing clinical features. It may be mentioned that in the majority of these cases one or more question marks had been added to the diagnosis.



Fig 2. Geographic distribution f new cases of pulmonary sarcoidosis hospitalized in Finland in 1960

In 1967 patients with sarcoidosis were treated at 64 hospitals. Data for the present study were obtained from 61 of these. Of the three hospitals which did not place their records at the writer's disposal, two were local hospitals with one case each. These two patients were, however remitted to other

hospitals and are thus included in the present series. The third hospital not responding to the request for data was a sanatorium, at which four patients were treated under the diagnosis of sarcoidosis. Thus, data were not available concerning only four patients. The patients with definite or highly probable sarcoidosis admitted to the above-mentioned 61 hospitals numbered 278. Of these, 58 were previously diagnosed and 220 were new cases. The geographical distribution of the new cases is shown in Fig. 3. Many patients were treated at two different hospitals. In 40 cases a diagnosis of sarcoidosis could not be accepted owing to inadequacy of the investigations performed or because it was obviously erroneous.

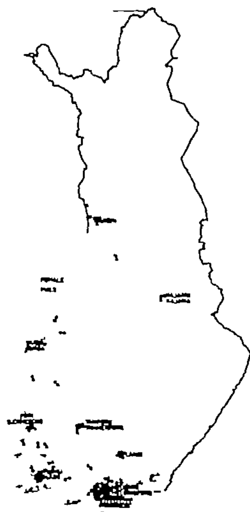


Fig. 3. Geographic distribution of new cases of pulmonary sarcoidosis hospitalized in Finland in 1967.

The age and sex distribution of the newly detected sarcoidosis patients admitted to Finnish hospitals in 1960 and 1967 appear in Table III. The sex ratio was practically the same in the two years in question, i.e. 65 per cent women in 1960 and 66 per cent in 1967. As may be seen in Table IV which shows the percentual age distribution of the cases, the age group 40—49 was the largest (28 per cent) among the female patients in 1960 while the age group 30—39 was the largest (31 per cent) in 1967. Over both years only about 20 per cent of the patients were under 30 and 10 per cent over 60 years of age.

Table III. Sex and age distribution of new cases of sarcoidosis admitted to Finnish hospitals in 1960 and 1967

Age	1960			1967		
group	Women	Men	Total	Women	Men	Total
—19	1	1	2	0	0	0
20—29	6	3	9	22	4	46
30—39	7	7	14	44	27	71
40—49	10	4	14	28	10	38
50—59	7	3	10	33	9	42
60—	5	1	6	19	4	23
Total	36	19	55	146	74	220
Per cent	65	35	100	66	34	100

Table IV. Percentual age distribution of new cases of sarcoidosis admitted to Finnish hospitals in 1960 and 1967

Age	1960			1967		
group	Women	Men	Total	Women	Men	Total
—19	3	5	4	0	0	0
20—29	17	16	16	15	32	21
30—39	19	37	5.5	31	37	32
40—49	28	21	25.5	19	14	18
50—59	19	16	18	22	12	19
60—	14	5	11	13	5	10
Total	100	100	100	100	100	100

The acceptability of the diagnosis appears in Table V. In 1960 the clinical diagnosis was histologically confirmed in over half the cases (60 per cent), while the diagnosis was based on the clinical picture alone in 36 per cent. The diagnosis was confirmed by a Kveim test in only 4 per cent. In 1967 the diagnosis was based on the clinical picture alone in only 15 per cent of the cases. The diagnosis was confirmed by histological investigation alone in 50 per cent and in 35 per cent by a Kveim test.

The number of new cases diagnosed in 1967 was four times higher than in 1960. The figure for 1967, i.e. 220, is in good agreement with the annual inci-

Table V Acceptability of diagnosis in new cases of sarcoidosis admitted to Finnish hospitals in 1960 and 1967

Group	Clinical picture	Kveim test	Biopsy result	1960 N of pat.	Per cent	1967 N of pat.	Per cent
I	Consistent with sarcoidosis	Positive	Positive	0		40	18
II A	»	Positive	Negative	0		17	8
II B		Positive	Not performed	2	4	20	9
III A		Negative	Positive	3	5	26	12
III B	»	Not performed	Positive	30	55	84	38
IV A		Negative	Negative	0		4	2
IV B		Negative	Not performed	0		1	0.5
IV C		Not performed	Negative	6	11	16	7
IV D		Not performed	Not performed	14	25	12	5.5
Total				55	100	220	100

dence of 40 new cases calculated for the whole country on the basis of the data for 12 tuberculosis dispensary districts during the period 1962—1967 Considering the results of the incidence and prevalence studies it would, however be obviously erroneous to conclude from the observations made on the two hospital series that the frequency of sarcoidosis had increased by four from 1960 to 1967 Very likely a considerable number of cases had escaped recognition in 1960 owing to insufficient knowledge of the clinical features of sarcoidosis. In addition, in 1967 improved diagnostic methods were available including, for instance, the Kveim test and mediastinoscopy This is clear from Table V which shows the acceptability of the diagnosis in the two years in question. Definite conclusions concerning a real increase can only be drawn from a study covering a longer period during which the same diagnostic opportunities have been available.

DISCUSSION

The frequency of sarcoidosis in many parts of the world is unknown. On the basis of 350 U.S.Army cases, Michael et al. (1950) noted a prevalence of 0.9 per/100,000 whites and 17.8 per/100,000 negroes. Gentry et al. (1955) observed a concentration of cases in the southeastern parts of the U.S.A. A similar geographical distribution was reported by Cummings et al. (1956), who also found that sarcoidosis was 13 times more frequent among negroes than among whites in a study comprising 1,194 cases. Cooch (1961) analysed sarcoidosis in the U.S.Army in 1952—1956 and reported a mean incidence of 11 new cases per 100 000 men. The highest rate was noted in the 25—29 age group. The ratio negroes: whites ranged from 10:1 to 45 1 Cooch, too, found that the disease was most prevalent among subjects born in the southeastern parts of the country Moreover the prevalence of sarcoidosis appeared to be higher among subjects born in rural districts than among those born in cities. Chapman (1964) summarized the epidemiological findings in the U.S.A. as follows: » ecological factors in sarcoidosis seem to include broadly the Southeast, the Great Lakes area and New England, an ethnic basis, a rural background with perhaps significant association with farm animals or pine forests; a trend toward familiar frequency and perhaps a peculiarly local pocketing that may be independent of kinship.» By contrast, Terris and Chaves (1966) observed no correlation with a previous southeastern domicile in a series of 40 biopsy proved cases, nor were they able to demonstrate any other correlations (pine forest, chewing soap, pitch or resin, clay eating, or exposure to specific crops or animals)

In Europe, the frequency of sarcoidosis seems to have been most thoroughly studied in Denmark, where a central register of sarcoidosis is run. Horwitz (1961) noted an annual incidence of 5.5 new cases per 100,000 of population during the period 1954—1957 The geographical distribution was uniform, apart from an area of Jutland, where the incidence was higher (11.6 per 100 000). Alsbirk (1964) reported an annual incidence of 3 4 per 100 000 during the period 1961—1962. He observed no regional variations. Later Horwitz (1967) published figures for the years 1962—1965 (994 cases). He gave an incidence of approximately 5 new cases per 100,000 but emphasized that many mild cases probably escaped recognition. Since evidently no corresponding central register of new cases is run in any other country comparable data are not available.

Most of the reported frequency figures are based on information collected at radiographic surveys of large population groups. Schönholzer (1947) noted a prevalence of 13 per 100,000 in a study of over 500,000 men in the Swiss Army In 1953, Bauer

reported high ratios for Sweden. In a 10-year radiographic study in Stockholm the prevalence was 30 per 100 000 in men and 50 per 100,000 in women. The highest rates were noted in the 25—29 age group: 90 per 100 000 in men and 110 per 100,000 in women. On the basis of studies carried out in 1950—1957 Wallgren (1958) estimated the prevalence of sarcoidosis in the whole of Sweden at 42 per 100 000

In a mass radiographic survey comprising over 450,000 persons in Liverpool, England, in 1959 Semple and Hughes (1959) noted a prevalence of 9 per 100,000 From Scotland, a prevalence of 6 per 100 000 was reported in 1957 in a survey of over one million individuals, and when over 750,000 subjects were examined in 1958 the corresponding figures was 5 per 100,000 (McGregor 1961)

From England and Wales, Anderson et al. in 1963 reported a prevalence of approximately 20 per 100,000 in mass radiography material. The overall ratio was the same for the two sexes, but for women of child-bearing age the prevalence was 39 per 100,000. The high prevalence of sarcoidosis among Irish people who had moved to London attracted special attention. The ratio was 200 per 100,000 in Irish women and 120 per 100,000 in Irish men.

In order to obtain an idea of the prevalence of sarcoidosis in different parts of the world, this subject was taken up by the Third International Conference on Sarcoidosis in Stockholm, 1963 Thirty reports from various parts of the world were presented. Many of the series were short and the studies were not uniform, but in review (Bauer and Löfgren 1964) they reflected the situation in general. The highest prevalence was reported from Sweden (55 per 100,000 and 64 per 100,000, respectively in two different studies). Ratios over 20 per 100 000 were also reported from Norway Eire and the Netherlands. A prevalence of over 10 per 100,000 but under 20 per 100,000 was reported from England, Northern Ireland, France, Germany Poland, Switzerland, Yugoslavia, Canada and New Zealand. Ratios under 10 per 100,000 were reported from Finland, Scotland, Czechoslovakia, Hungary Portugal, Argentina, Brazil, Uruguay Israel, Japan and Australia. In a separate investigation from New York City (Robins et al. 1964) it was stated that in a population consisting of 40 per cent or more negroes the prevalence of sarcoidosis was 64 per 100 000. When the proportion of negroes was between 20 and 39 per cent the prevalence of sarcoidosis fell to 32 per 100 000, and in groups less than 20 per cent negro the prevalence was lower still, i.e 17 per 100,000. The mean prevalence for the whole material, irrespective of race was 39 per 100,000

As compared to the above mentioned, earlier investigations it may be stated that the annual incidence of sarcoidosis observed in the present Finnish study i.e. 5.3 new cases per 100,000 of population, is in good agreement with the reliable studies performed in Denmark. A certain local variation was noticed, however the incidence being 9 1 per 100,000 within the tuberculosis district of Raseborg, 5 1 per 100 000 in the district of Vasa, 4 0 per 100,000 in the district of Kanta Häme and 3 8 per 100,000 in the tuberculosis districts of Pohjois-Pohjanmaa and Åland. According to this, the annual incidence of sarcoidosis would be about twice as high in the tuberculosis district of Raseborg in the southern and southeastern parts of the country as in the other districts investigated. It should, however be pointed out that the medical team in the tuberculosis district of Raseborg has been particularly interested in sarcoidosis since the end of the 1950's. Therefore, the possibility that in the other districts a greater proportion of cases has escaped recognition cannot be ruled out

In the present study of the radiographic prevalence of sarcoidosis the result for the whole country was 7.5 per 100 000 This would make Finland one of the countries considered at the Conference on Sarcoidosis in Stockholm to have a low prevalence of the disease (under 10 per 100 000). However as compared to the reports from other countries the above-mentioned figure for Finland is too low for two reasons. The present material includes only verified cases of sarcoidosis, while the majority of the reports cited above are based on suspected radiographic findings. In addition, the present results show a considerable local variation, the prevalence being 1—1 per 100 000 in the tuberculosis district of Raseborg, 9 1 per 100,000 in the district of Kanta-Häme, 7 8 per 100,000 in the district of Vasa, 3.5 per 100,000 in the district of Pohjois-Pohjanmaa and —3 per 100,000 in the tuberculosis district of Åland. As already stated this variation shows no correlation to the situation in regard to tuberculosis.

Although the tuberculosis district of Raseborg ranks at the top for the prevalence of sarcoidosis, the difference as compared to the Vasa and Kanta Häme districts is not so marked as in regard to the incidence of the disease. This seems to support the view that the figures for all districts except Raseborg might be too low The figures for Åland and Pohjois-Pohjanmaa are strikingly low

As already mentioned, in an area investigated with particular thoroughness (the tuberculosis district of Raseborg), a prevalence of somewhat over 10 per 100,000 radiographs was observed. The prevalence for the whole country does not attain this level. It is obvious that the prevalence of sarcoidosis in Finland is markedly lower than in neighbouring Sweden (Bauer 1953 Wallgren 1958, Bauer and Löf

gren 1964). In Norway too the prevalence seems to be more than twice as high as in Finland (Riddervold 1964). On the other hand, the Finnish results show considerable agreement with reports from Denmark (Horwitz 1961 1967) and England and Scotland (Semple and Hughes 1959 McGregor 1961) even though higher prevalence figures have been indicated in certain other British studies (Anderson et al. 1963) In reports based on military series, higher prevalence figures have as a rule been noted. This is accounted for by the fact that the series have been selected by age those age groups in which sarcoidosis is most prevalent being predominant.

CONCLUSION

The prevalence of pulmonary sarcoidosis was studied through the years 1962—1967 in mass radiography material from 12 tuberculosis dispensary districts in Finland, chosen so as to represent areas differing in regard to the tuberculosis trend. Verified pulmonary sarcoidosis was observed in 7.5 cases per 100,000 examined. A local variation was found, the highest prevalence (16.7 per 100,000) being noted in the Helsingfors dispensary district of the tuberculosis district of Raseborg and the lowest (2.3 per 100 000) in the tuberculosis district of Åland. No correlation with the situation in regard to tuberculosis was observed.

A study of the incidence of sarcoidosis, performed in 1962—1967 in the same areas as the prevalence study revealed an annual incidence of 5.3 new cases per 100,000 of population. A local variation was also observed in this investigation, with a peak (12.0 per 100,000) in the Helsingfors dispensary district of the tuberculosis district of Raseborg. The ratios noted did not correlate to the tuberculosis situation. On the basis of the incidence study a calculated figure of approximately 240 annual new cases was obtained for the whole of Finland. An investigation of hospital cases from 1960 and 1967 showed that 220 new cases of sarcoidosis were diagnosed in Finnish hospitals in 1967 which is in fair agreement with the above mentioned calculated figure. In 1960 only 55 cases were diagnosed. However on the basis of the present results it cannot be confidently maintained that sarcoidosis increased in Finland during the period 1960—1967 considering that the diagnostic methods had markedly improved by 1967 and that acquaintance with the clinical picture of the disease has steadily increased. The development can only be evaluated when adequate diagnostic facilities have been available for a long period of time.

As compared to the situation in other countries, it may be stated that the frequency of sarcoidosis in Finland is the same as in Denmark, but lower than in Norway and much lower than in Sweden. Even though it may be assumed that the figures noted in Finland are somewhat too low the level of the Swedish figures is not attained. In regard to the reports from other countries it should be pointed out that many studies have been based on suspected cases without verification, or on selected series. The results are therefore not quite comparable with those of the present study

IV THE CLINICAL PICTURE OF SARCOIDOSIS IN FINLAND

INTRODUCTION

The clinical picture of a disease may vary. The illness may affect particular age groups, and the incidence may be different in the two sexes. The morbidity is sometimes influenced by occupation and environment. The mode and time of presentation and other factors connected with the onset of the disease may be specific.

A disease potentially involving many organs may differ in different countries in regard to the organ distribution of the morbid changes. This applies in a high degree to sarcoidosis, which admittedly occurs both as an acute-subacute disease involving only a few organs and as a chronic illness affecting many organs.

The Kveim test performed with standardized antigen has proved to be specific in sarcoidosis. This test is also an indicator of the activity of the illness, the result being often positive in active cases and negative in chronic, stationary disease. Hence, the rate of Kveim-positive sarcoidosis patients reflects the situation in the population studied.

Tuberculin negativity, hyperproteinaemia, changes in the electrophoretic pattern of the serum proteins, hypercalcaemia and hypercalciuria are frequent findings in sarcoidosis. Their reported frequencies have varied, however.

An analysis of the above-mentioned and other factors associated with sarcoidosis will clarify the nature of sarcoidosis as it appears in Finland.

MATERIAL

The series studied consists of 140 patients with sarcoidosis admitted to the Mjölbolsta Hospital and the Fourth Department of Medicine, Helsinki University Central Hospital. Mjölbolsta Hospital is the central sanatorium of the tuberculosis district of Raseborg, a region in south and southwestern Finland with about 220,000 inhabitants. The district in question consists of 24 rural municipalities and eight towns or townships. In addition, a further two rural municipalities and the city of Helsinki/Helsingfors are entitled to beds in the hospital. The Helsinki University Central Hospital is owned by a municipal association consisting of 31 rural municipalities and 13 towns or townships in south Finland. Of the municipalities entitled to beds at Mjölbolsta Hospital, only one township and nine rural municipalities are not members of the Helsinki University Central Hospital municipal association.

During the period covered by the present study i.e. 1959—1967 practically all patients suspected of sarcoidosis in the tuberculosis district of Raseborg were admitted to the Mjölbolsta Hospital for more thorough investigation and diagnosis. This also applies to asymptomatic cases. Hence, the present series is representative for the region in question. Sixty-nine per cent of the patients came from the tuberculosis district of Raseborg. Since the remaining patients showed no deviating characteristics, the whole material is treated as one series.

For the sake of a more complete understanding of the nature of sarcoidosis in Finland, the hospital records *of all patients admitted to Finnish hospitals* in 1960 and 1967 were studied, as stated in Chapter III. The clinical picture in these cases was found to be the same as in the above-mentioned more thoroughly investigated series. This series may thus be considered representative for the whole country.

Verification of the diagnosis of sarcoidosis

In the verification of diagnosed cases of sarcoidosis attention was paid to the three criteria postulated by the Second International Conference on Sarcoidosis in Washington, D.C., in 1960, i.e. a typical clinical picture, a positive Kveim test and a positive biopsy specimen.

The *clinical picture* was considered typical of sarcoidosis when in acute cases erythema nodosum or joint symptoms were present in association with bilateral hilar node hyperplasia (BHL = bilateral hilar lymphoma syndrome). Subacute cases were accepted as sarcoidosis in the presence of BHL with or without perihilar diffusedly miliary or partially confluent pulmonary infiltration. In protracted cases tending to become chronic, chest radiography revealed fibrosis of varying degree. Attention was also paid to cicatricial reactions, a decreased tuberculin sensitivity the possible occurrence of uveitis and other extrathoracic sarcoidosis. Changes in the electrophoretic pattern of the serum proteins consistent with sarcoidosis, disturbances in the calcium-phosphorus metabolism and renal calcification were also taken into account. As regards the differentiation of sarcoidosis from tuberculosis, attention was paid to repeatedly negative tb cultures, spontaneous regression of the pulmonary manifestations and the result of antituberculotic or glucocorticoid treatment, when such had been given.

Kveim's test was not performed in the years 1959–1962 because of the lack of test material. During the period 1963–1966 the test was performed with antigen kindly placed at disposal by Professor Louis E. Siltzbach, New York. Biopsy was performed on the papules, and the histopathological findings were evaluated by the pathologists of the respective hospitals, Siltzbach and the present writer In 1967 antigen delivered by Dr T H. Hurley Melbourne, was also used.

Tissue biopsy specimens were obtained in as many cases as possible and specimens were taken from various organs. The finding was considered as evidence of sarcoidosis when productive epithelioid cell granuloma with no or only slight necrosis was demonstrated.

On the basis of the above-mentioned three criteria the patients were classified as shown in Table VI in the nine groups which emerge when the clinical picture is consistent with sarcoidosis and the result of the Kveim test and biopsy respectively is either positive, negative or lacking. As may be seen in the table a clinical diagnosis of sarcoidosis was supported by a positive Kveim test and/or a positive biopsy result in 117 cases, while such confirmation was lacking in 23 cases. These were nonetheless included in the series because of a very convincing clinical picture

Table VI. Acceptability of the diagnosis of sarcoidosis.

Group	Clinical picture	Kveim test	Biopsy result	No of pat.
I	Consistent with sarcoidosis	Positiv	Positive	45
II A		Positiv	Negativ	26
II B		Positive	Not performed	8
III A		Negativ	Positive	8
III B		Not performed	Positiv	30
IV A		Negativ	Negative	10
IV B		Negative	Not performed	1
IV C		Not performed	Negativ	5
IV D		Not performed	Not performed	7
Total				140

RESULTS AND DISCUSSION

Sex ratio

The series consists of 45 men and 95 women. The ratio men. women is 1 2.1 Two of the patients were brothers. The remainder were not related. A sister of one of the female patients, not included in this series, had had sarcoidosis.

In connection with the Third International Conference on Sarcoidosis in Stockholm, 1963 Bauer and Löfgren (1964) surveyed the epidemiological data from mass radiographic surveys carried out in 25 countries. They concluded that »the distribution of pulmonary sarcoidosis between the sexes is diverse, and does not indicate any preponderance of either sex»

To permit comparison of the present series with those previously reported representative series from different countries have been compiled in Table VII. The sex ratio in the present study (68 per cent women) is the same as in an earlier Finnish investigation (Putkonen et al. 1965a). As regards Scandinavia, a similar sex ratio has been observed in Sweden. Löfgren and Lundbäck (1952a) reported a somewhat higher ratio of women (76 per cent women) in patients with BHL, while Hedvall (1960) and Rudberg-Roos (1962) noted somewhat lower figures (62 and 57 per cent women, respectively) in series also including patients with chronic sarcoidosis. On the other hand, Horwitz (1967) reported a sex ratio of about 1 1 in an extensive study comprising the whole of Denmark. A lower involvement of women than in the present series was also observed in Norway (Riddervold 1964).

As regards other European countries, female patients are predominant in all series, apart from a French report (Turiaf et al. 1964), in which the proportion of women was only 40 per cent. The highest proportion of women is encountered in a Scotch series: 79 per cent (Douglas 1961). Over 50 per cent women though less than in the present series, has been reported from England (Cowdell 1954 Scadding 1967) the Netherlands (Orie and Ter Brugge 1964) and Belgium (Lebacq 1964).

Table VII Sex and age distribution in series of sarcoidosis from different countries.

Country and author	Year	No. of pat.	Women Per cent	Negroes Per cent	Percentual age distribution —19	20—29	30—39	40—49	50—59	60—
Sweden										
Löfgren and Lundbäck	1952	12	76	0	0.5	44	40	10	4	1.5
Hedvall	1960	142	64	0	1	18	22	[illegible]8	20	11
Rudberg Roos	1962	[illegible]96	57	0						
Finland										
Putkonen et al	1965	94	68	0						
Denmark										
Horwitz	1967	994	c. 50							
Norway										
Riddervold	1964	209	57							
England										
Cowdell	1954	90	51	0	17	6	24	18	11	4
Scadding	1967	275	57		6	50	7	14	3	1)
Scotland										
Douglas	1961	100	79							
The Netherlands										
Orie and Ter Brugge	1964	994	63							
Belgium										
Lebacq	1964	100	56		4	32	37	[illegible]0	5	
France										
Turiaf et al.	1964	268	40							
Japan										
Nobechi	1964	28[illegible]	49	0	18	47	16	9	6	unknown
Uruguay										
Purriel et al	1964	90	51		6	26	16	[illegible]3	22	7
U.S.A.										
Longcope and Freiman	195[illegible]									
Baltimore		90	47	81	19	44	14	10	7	6
Bost		52	77	15		21	33	31	1	2
Carr and Gage	1954	194	61	5	5	17	29	19	22	8
Israel and Sones	1958	160	66	86						
Mayock et al.	1963	145	63	70	15	35	21	14	10	5
Terris and Chaves	1967	240	74	74	3	39	31	18	7	
Siltzbach	1967	311	68	47	71 per cent under 40 years					
Present series		140	68	0	0.5	20	31	28	17	3.5

) Age distribution by groups —[illegible]0 1—30, 31—40, 41—50, 51—60 61—

In Japan (Nobechi 1964) and Uruguay South America (Purriel et al. 1964), a sex ratio of 1 1 has been noted In North American series the proportion of women ranges from 47 to 77 per cent. Longcope and Freiman (1952) gave a ratio of 47 per cent women in a series from Baltimore in which the majority were negroes, while in a series from Boston with only 15 per cent negroes the women constituted 77 per cent. Obviously the sex ratio is not however dependent on race since Carr and Gage (1954) had 61 per cent women in a series with only 5 per cent negroes, while Israel and Sones (1958) reported a ratio of 66 per cent women in a series with 86 per cent negroes. In a series from New York including 47 per cent negroes, Siltzbach (1967a) reported a sex ratio of 68 per cent women This is in agreement with the present series. In other studies, in which the patients were negroe to 70—74 per cent (Mayock et al. 1963 Terris and Chaves 1967), a similar sex ratio was noted (63 per cent and 74 per cent women, respectively)

Conclusion Just as in most other countries, in Finland the morbidity in sarcoidosis is higher in women than in men. The sex ratio (68 per cent women) is the same as in Sweden and some other European countries and in certain reports from the U.S.A. The proportion of women is definitely higher however than in some series published in France, Japan, Uruguay and Denmark. A markedly higher proportion of women has been noted in Scotland.

Age distribution

The age distribution in the present series is shown in Table VIII. Among the men the 30—39 age group is the largest, and the mean age of the men is 34.7 years (range 21—63 years) Among the women the 40—49 age group is the largest, and the mean age of the women is 42.2 years (range 19—66 years). The mean age in the total series is 39.8 years. The percentual age distribution in the total series is shown in Fig 4

Table VIII. Age distribution of 140 patients with pulmonary sarcoidosis.

Age group	W men	Men	Total
–19	1	—	1
20–29	13	15	28
30–39	25	18	43
40–49	30	9	39
50–59	22		24
60–	4	1	5
Total	95	45	140

Mean ge f the women 42.2 years
Mea age of the men 34 7 years
Mean ge of the total series 39.8 years

In many surveys of sarcoidosis it is stated that the disease as a rule commences at an age of 25–30 years. In series based on mass radiographic surveys a tendency towards a greater predominance of the younger age groups is common, as compared to hospital series consisting of patients usually examined on account of symptoms. In the latter the proportion of older age groups is greater Sarcoidosis in children is considered relatively rare.



Fig 4 Percentual age distribution f 140 patients with pulmonary sarcoidosis.

In a survey of over 3 000 reported cases of sarcoidosis, Mc Govern and Merritt (1953) found only 104 patients under 15 years old. They added nine cases of their own. Of the total 113 28 patients were under nine years old, the remainder being between nine and 15 In a Hungarian series (Mandi 1964b) comprising 96 patients, 14 were under 15 years old. The majority had been detected by mass chest radiography The present series comprises no patient under 15 although mass radiographic surveys have also been carried out among school children.

The percentual age distribution in a number of reports containing sufficiently detailed data is shown in Table VII In the 12 series, the age group 20–29 years is the largest in eight, the 30–39 group is the largest in three and the 40–49 group in one (Hedvall 1960). In three series (Carr and Gage 1954 Hedvall 1960 Purriel et al. 1964), the 50–59 age group represents 20–22 per cent of the patients. In all series few patients are over 60. This age group is most numerous (11 per cent) in Hedvall's series (1960). In all series the age distribution is the same in the two sexes.

In the present series, which includes all known cases irrespective of the mode of detection, the 30–39 age group is the largest and the 40–49 group the next largest. The group 20–29 years is the third (20 per cent). The 50–59 group is almost equally large (17 per cent) As compared to other series in only two (Carr and Gage 1954 Hedvall 1960), is the 20–29 group relatively smaller and in only one (Longcope and Freiman, Boston 1952) is the 40–49 group relatively greater Broadly speaking, the age distribution in the present series is the same as in the last mentioned three reports.

Conclusion. On the basis of the present series it may be stated that in Finland the age distribution of sarcoidosis shows a tendency towards involvement of older age groups as compared to other countries. Only 20 per cent of the patients were aged 20–29 This tendency is more marked among the women. In both sexes together the 30–39 age group is the largest while among the women the 40–49 group is the largest.

Environmental background

Ninety-seven patients (69 per cent) came from the tuberculosis district of Raseborg, 37 came from the city of Helsinki/Helsingfors, and six from other municipalities outside the tuberculosis district. Of the 45 men in this series, 25 (56 per cent) lived in population centres and 20 (44 per cent) in rural municipalities. Of the women, 55 (57 per cent) lived in population centres and 40 (43 per cent) in rural municipalities. Of the total series, 80 patients (56 per cent) lived in an urban environment and 60 (44 per cent) in rural areas.

In the hope of detecting factors possibly predisposing to sarcoidosis, the environmental background of the patients has been the object of thorough investigation. No definite correlations have been observed. In many studies from the U.S.A. (e.g Gentry et al. 1955 Buck 1961) sarcoidosis has been found to be more prevalent in rural populations than in urban groups, and Chapman (1964) concluded that »a rural background with perhaps significant asso-

ciation with farm animals or pine forests» exists. An entirely different distribution was reported in a French series (Turiaf et al. 1964) in which 78 per cent of the patients had an urban background.

Bauer and Löfgren (1964), in a survey of mass radiography data from [illegible]5 countries, concluded. »In spite of local variations the reports do not disclose striking differences between prevalence rates of urban and rural populations.»

Of the present series of patients, 56 per cent lived in population centres and 44 per cent in rural areas. As estimated on the population census, the prevalence is somewhat higher in the rural than in the urban population, but the difference is not significant.

Conclusion. The distribution of sarcoidosis between urban and rural areas is uniform, just as has been reported from many other countries. In contrast to the situation in the U.S.A. no tendency towards predominance of patients with a rural background was observed, nor were urban elements predominant as was the case in a French report.

Modes of presentation

Fifty-five patients (26 men and 29 women), i.e. 39 per cent of the total series, were symptom-free when they were admitted to hospital on account of a suspected routine chest radiograph. Of these patients one had recurrent sarcoidosis, while in the remaining 54 cases the disease was discovered for the first time. The composition and age distribution of this group of patients are shown in Table IX. It is striking that men predominate among those who were symptom-free when first seen. Of all male patients, 58 per cent belong to this group, against 30 per cent of the women. The age groups 20—29 and 30—39 are the largest among the men. On comparison with the corresponding female age groups a definite sex difference is observed.

Table X shows the age distribution among the 85 patients (19 men 66 women) admitted to hospital on account of subjective symptoms (61 per cent of the total series). Sarcoidosis had previously been diagnosed in seven of these patients. The majority of the female patients in all age groups showed subjective symptoms when they first came under medical observation. Seventy per cent of all women belong to this group.

The symptoms of the above-mentioned 85 patients are compiled in Table XI. As may be seen in the table erythema nodosum (EN), joint symptoms, fever and fatigue are predominant among the women. Respiratory symptoms, on the other hand, occur in proportion to the sex ratio.

The subjective initial symptoms in the 78 newly discovered cases are compiled in Table XII. Only one symptom per patient, i.e. that with which the patient presented, has been included. The predominance of EN as an initial symptom in female patients is striking. Otherwise no significant differences were observed between the sexes.

The various sarcoidosis series described differ considerably in regard to the grounds on which patients have been selected for study. Hospital series consist almost exclusively of patients admitted on account of subjective symptoms. Series collected on the basis of compulsory mass radiographic surveys contain a high proportion of symptom-free patients at a less advanced stage of the disease.

The present series comprises all cases discovered during the period 1959—1967 within a defined

Table IX. Age and sex distribution of 55 symptom-free sarcoidosis patients admitted to hospital on account of suspected chest radiographs. In each group the number of patients is indicated in relation to the total number of patients in the same group.

Age group	—19	20—29	30—39	40—49	50—59	60—	Total	Per cent
Men	0/0	11/15	10/18	3/9	[illegible]/2	0/1	26/45	58
Women	0/1	3/13	9/25	8/30	8/22	1/4	29/95	30
Total	0/1	14/28	19/43	11/39	10/24	1/5	55/140	39

Table X. Age and sex distribution of 85 sarcoidosis patients with subjective symptoms. In each group the number of patients is indicated in relation to the total number of patients in the same group.

Age group	—19	20—29	30—39	40—49	50—59	60—	Total	Per cent
Men	0/0	4/15	8/18	6/9	0/2	1/1	19/45	4
Women	1/1	10/13	16/25	[illegible]2/30	14/22	3/4	66/95	70
Total	1/1	14/28	4/43	[illegible]8/39	14/24	4/5	85/140	61

Table XI. Subjective symptoms on account of which 85 patients with sarcoidosis were admitted to hospital.

Symptom	Women	Men	Total
Respiratory tract			
Dyspnoea	15	8	23
Cough, bronchitis	12	3	15
Chest pain	3	—	3
Nose blocked	1	—	1
Sore throat	2	—	2
Erythema nodosum	35	7	42
Joint symptoms			
Joint pain	14	3	17
Painless joint swelling	4	2	6
Fever	22	3	25
Fatigue, impaired general condition	14	3	17
Weight loss	1	1	2
Ocular symptoms	3	2	5
Enlargement of peripheral nodes	1	1	2
Facial paresis	—	1	1
Renal colic	1	1	2
Skin eruption	1	—	1
Alopecia	1	—	1
Thirst	—	1	1

Table XII. Main symptoms on admission in 78 cases of sarcoidosis not previously diagnosed.

Main symptom	Women	Men	Total
Respiratory tract			
Dyspnoea	7	3	10
Cough, bronchitis	5	2	7
Chest pain	1	—	1
Nose blocked	1	—	1
Erythema nodosum	27	2	29
Joint symptoms			
Joint pain	10	3	13
Painless joint swelling	—	1	1
Fever	3	2	5
Fatigue, impaired general condition	6	2	8
Ocular symptoms (uveitis)	1	1	2
Facial paresis	—	1	1
Total	61	17	78

geographical area, irrespective of the mode of detection. It has therefore been compared to series collected on the same principles.

The most thorough study of early sarcoidosis is the one published by Löfgren and Lundbäck (1952a b). In their series of 212 patients with BHL, 70 (38 women, 32 men), or 33 per cent, had been summoned for investigation because of the signs revealed by compulsory mass chest radiography. EN was the presenting symptom in 113 cases (107 women, 6 men) or 53 per cent, while 29 patients presented with some symptom other than EN. The sex distribution was strikingly uniform in both the asymptomatic group and the group showing symptoms other than EN. On the other hand, in the group with EN the predominance of women was very marked. Hedvall (1960), in another investigation from Sweden, reported that of 142 sarcoidosis patients, 50 (35 per cent) had been detected at mass radiographic survey.

In James' (1956) series of 150 patients with histologically verified sarcoidosis, 19 per cent were discovered by routine chest radiography, 23 per cent showed EN with or without polyarthritis, in 11 per cent the disease commenced with iridocyclitis, in 10 per cent with skin changes and in 10 per cent with peripheral lymphadenopathy and/or splenomegaly.

Of 125 patients from London, studied by Smellie and Hoyle (1960), 58 (46 per cent) were detected at mass radiographic survey. Symptoms from the respiratory tract were present in 26 cases (21 per cent), uveitis in 18 cases (14 per cent) and EN in only 12 cases (10 per cent).

Putkonen (1966), in a series consisting of 85 Kveim-positive patients with subacute sarcoidosis, analysed the symptoms on account of which the remitting physician had suspected sarcoidosis. An abnormal chest radiograph was the only sign of the disease in 27 per cent of the cases, EN in 40 per cent, uveitis and/or parotitis in 12 per cent, respiratory symptoms in 9 per cent, skin manifestations other than EN in 7 per cent and other symptoms in 5 per cent. As regards the distribution, it must be taken into account that Putkonen was Head of a dermatological clinic.

In Scadding's (1967) series of 275 patients with sarcoidosis, 94 cases (48 female, 46 male), or 34 per cent, had been discovered by mass radiographic surveys or other routine investigations. In 31 cases (25 female, six male), or 11 per cent, EN was the presenting symptom. The disease commenced with ocular symptoms in 27 cases, or 10 per cent, and with skin manifestations in 15 cases, or 5 per cent.

In series from the U.S.A. patients with subjective symptoms are predominant. Entirely symptom-free patients, whose disease was discovered by mass chest radiography, constituted 8–13 per cent in different reports (Longcope and Freiman 1952, Israel and Sones 1958, Cummings et al. 1959, Mayock et al. 1963). EN was a rare finding in these studies, being observed in 3 per cent (Mayock et al. 1963) and 2 per cent (Israel and Sones 1958). Siltzbach's (1967a) series of 311 patients constitutes an exception, inasmuch as 40 per cent were discovered by routine chest radiography. In 19 per cent the disease was

detected because of respiratory symptoms, 11 per cent presented with EN 7 per cent with ocular symptoms, 6 had skin manifestations and 5 per cent showed peripheral lymph node enlargement. Another 11 kinds of symptom occurred in lower proportions.

In the present series 39 per cent of the patients were symptom-free and the disease was discovered by mass chest radiography The sex distribution in this group was uniform: 29 women and 26 men. This is in good agreement with the figures reported by Löfgren and Lundbäck (1952a) Siltzbach (1967a) and Scadding (1967). Of the total number of male patients 58 per cent were symptom-free when their illness was detected. The corresponding figure for the female patients is 30 per cent. The tendency is the same as in the series of Löfgren and Lundback, in which 63 per cent of the male cases and 24 per cent of the female cases were detected at mass radiographic survey In Scadding s series from England the distribution was more uniform, 38 per cent of the men and 31 per cent of the women being investigated because of routine radiographic findings. On comparison with the other two investigations published by British authors (James 1956 Smellie and Hoyle 1960) which contain no data concerning the sex distribution, it is found that the proportion of asymptomatic cases is definitely lower in James series (19 per cent) and somewhat higher in the series of Smellie and Hoyle (46 per cent) In an earlier Finnish investigation (Putkonen 1966) the proportion of symptom-free patients with abnormal chest radiographs was only 27 per cent, which is markedly lower than in the present series. It should be borne in mind, however that Putkonen s series was derived from a dermatological clinic, and asymptomatic cases detected at compulsory mass radiographic surveys are as a rule first remitted to chest clinics for thorough investigation.

In the present series, the largest group of the cases detected because of subjective symptoms consisted of patients showing EN These numbered 29 (27 women and two men) and constituted 22 per cent of the total series. The sex ratio is the same as in the series of Löfgren and Lundbäck, but the total number of cases is definitely lower The rate of EN is the same as that reported by James. As compared to the other two English series (Smellie and Hoyle 1960 Scadding 1967) and the North American series the frequency of EN as a presenting symptom is higher in the present series. Putkonen (1966) observed EN in 40 per cent of his series of subacute sarcoidosis. The higher frequency in Putkonen's Finnish series as compared to the present one is accounted for in part by the different composition of the two (Putkonen's series consisted exclusively of subacute cases) and in part by the fact that patients with skin manifestations are more often primarily remitted to a dermatological clinic.

In the present series 19 patients (14 per cent) presented with respiratory symptoms. This is a somewhat lower rate than in a study from the U.S.A. and two British investigations, in which the corresponding figures were 19 per cent (Siltzbach 1967a), 21 per cent (Smellie and Hoyle 1960) and 28 per cent (Scadding 1967) On the other hand, 9 per cent of James (1956) patients showed respiratory distress when first seen. As compared to Putkonen s Finnish series, respiratory symptoms were more frequent in the present series (14 per cent in the latter 9 per cent in the former)

In 14 cases (10 per cent) the disease commenced with joint symptoms. James did not specify the frequency of polyarthritis, he only gave a figure for EN and stated that some of the patients with EN also had joint symptoms. The chronological order of the symptoms was not indicated. Smellie and Hoyle observed polyarthritis as the initial symptom in only one patient of 125 and Scadding noted »febrile arthralgia» as the first symptom in eight patients (3 per cent) Siltzbach likewise gave a frequency figure of 3 per cent for arthralgia as the presenting symptom.

Fever as the only initial symptom occurred in the present series in five cases (4 per cent). Scadding noted three similar cases (1 per cent), while neither James nor Smellie and Hoyle reported any similar case.

Fatigue and subjectively poor condition were the first symptoms in eight (6 per cent) of the present patients The corresponding figures given by James and Scadding are 5 and 3 per cent respectively Siltzbach indicated »fever weight loss, weakness» as the presenting symptoms in 3 per cent of cases.

Ocular manifestations were first observed in only two patients (1.5 per cent). James corresponding figure was 11 per cent and Smellie and Hoyle had 14 per cent. This is in part accounted for by the fact that James was particularly interested in ocular sarcoidosis and Smellie and Hoyle co-operated closely with an eye clinic. However Scadding noted ocular disease in 10 per cent of his patients when first seen, Siltzbach in 7 per cent and Putkonen in 12 per cent. The last-mentioned figure includes patients showing parotitis alone.

Parotitis and facial paresis were observed in one of the present cases, and Smellie and Hoyle likewise reported one case while James series included four cases and Siltzbach s series six cases (2 per cent) with these initial clinical features.

Conclusion. The initial features of sarcoidosis noted in the present series are consistent with what has previously been observed by Swedish and British

investigators. About 40 per cent were symptom-free cases discovered at mass radiographic surveys. Relatively speaking, men were more numerous than women in this group. Among the patients showing symptoms, those with EN constitute the largest group (22 per cent), with a predominance of women. However EN is a definitely less common initial symptom than in Sweden, though the ratio is the same as in British series or somewhat higher Joint symptoms alone are more frequent than in the investigations referred to for comparison, while ocular disease is markedly less common as the symptom first observed.

As compared to an earlier Finnish series (Putkonen 1966) consisting solely of subacute cases of sarcoidosis, differences are observed in regard to the initial features. These are accounted for by the fact that the series in question was collected at a dermatological clinic.

Time of onset of sarcoidosis

The month in which the disease commenced in the 85 patients showing symptoms appears in Table XIII. The time of onset is separately indicated for the patients presenting with EN As may be seen in the table, a striking number of women fell ill in the months of April and May- 25 of those 57 (44 per cent) for whom the time of onset could be definitely established. A uniform distribution over the months of the year would imply four to five new female patients per month. The preponderance for April and May is due to the fact that half the patients with EN (17 of 34) fell ill during these months. In regard to 10 cases the time of onset could not be definitely established. This group includes those patients who had previously diagnosed sarcoidosis when they were admitted to hospital.

Table XIII also shows the time of the year when the asymptomatic cases were discovered. These were evenly distributed over the different months and the monthly numbers show a relationship to the number of persons attending mass radiographic surveys.

A concentration of EN in spring has previously been observed by James (1961a) who found that the majority of patients with EN due to sarcoidosis fell ill in March — May The same seasonal variation was noted in regard to EN due to other factors. Hannuksela (1965) also showed that the seasonal variation involved is not specific for sarcoidosis there is a concentration of EN in spring which is independent of the etiology

Relationship between the onset of sarcoidosis and pregnancy — lactation

In two patients sarcoidosis was observed in the fifth and sixth months of pregnancy respectively A further six patients fell ill within a year from delivery and one fell ill six months after lactation had been discontinued.

On the one hand, it is known that sarcoidosis often commences or recurs after delivery or abortion. On the other hand, if a sarcoidosis patient becomes pregnant, this often has a favourable effect on the disease (Franz and Wurm 1962, Löfgren 1967 Winnacker et al. 1968) Franz and Wurm analysed 48 pregnancies in 41 women with sarcoidosis. These cases had been detected during a 10-year study comprising a total of 1,200 sarcoidosis patients. In two-thirds, improvement of pulmonary sarcoidosis was observed during pregnancy In eight cases the pulmonary state remained stationary and in the remainder the situation could not be confidently evaluated owing to lack of a sufficient number of chest radiographs. In another 22 cases sarcoidosis commenced after the completion of pregnancy

Table XIII. Time of onset of sarcoidosis in patients showing symptoms, separately in patients with erythema nodosum and time of discovery of asymptomatic cases.

		Calendar month I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Uncertain
Patients with symptoms	Men	1	4	3	3	—	1	1	—	1	—	—	3	2
	Women	6	3	6	10	15	3	—	2	—	6	4	3	8
	Total	7	7	9	13	15	4	1	2	1	6	4	6	10
Patient with erythema nodosum	Men	—	2	—		—	—	1	—	1	—	—	1	—
	Women	5	2	3	7	10	2	—	1	—	3		—	—
	Total	5	4	3	9	10	2	1	1	1	3	2	1	—
Symptom-free patients	Men	2	2	4	3	3	3	2	—	1	—	5	—	1
	Women	3	4	3	1	—	3	2	1	4	2	3	2	1
	Total	5	6	7	4	3	6	4	1	5	2	8	2	2

within six months in 11 cases, within six to 1 months in 11 According to Löfgren and Lundbäck (1952a), in 24 out of 107 female sarcoidosis patients showing EN and BHL, EN commenced during the period of lactation, with a peak in the fifth month after delivery; in three cases EN commenced during pregnancy In addition, their series contained five patients whose sarcoidosis commenced within a year from delivery but after the discontinuation of lactation. Thus, a relationship between the onset of sarcoidosis and a completed pregnancy was observed in about 30 per cent of the cases. Among 54 patients showing BHL but not EN a similar relationship was found in only seven cases.

The present series contains two female patients whose sarcoidosis was observed during pregnancy One of them showed only BHL, while slight miliary parenchymal infiltration was also noted in the other case. It is unknown, however whether these patients had normal chest radiographs immediately before pregnancy In six cases sarcoidosis commenced within a year from delivery Three of these patients presented with EN Of the remaining three patients two had attended mass radiographic surveys during pregnancy and the findings had been normal. When sarcoidosis was diagnosed, the pulmonary findings corresponded to stage I in five cases, to stage II in one. In the latter EN was not present and the patient had not been examined during pregnancy For this reason no definite relationship with pregnancy can be established in this case. An obvious connection between pregnancy and the onset of sarcoidosis was thus observed in less than 10 per cent of the cases. It is striking that a relationship between the onset of sarcoidosis and pregnancy is less frequent in the present series than in that of Löfgren and Lundbäck, in which the mean age of the female patients was markedly lower This seems to argue in favour of the view that pregnancy and lactation are not primary eliciting causes of sarcoidosis.

Duration of sarcoidosis before diagnosis

The Second International Conference on Sarcoidosis, Washington D C. 1960 recommended the classification of sarcoidosis by known duration and suggested a division according to whether the duration was known to be less or more than two years.

Since all patients in the present series showed intrathoracic changes, an attempt was made to estimate the duration of the disease on the basis of earlier chest radiographs. Twenty patients had had normal radiographs within a year and 43 patients within two years before sarcoidosis was diagnosed. In 34 cases changes had been present for at least two years in six of these, there had been changes for at least five years. In 43 cases the duration of the disease could not be established owing to the lack of radiographic evidence. The last-mentioned group being relatively large (31 per cent of the total series), it was not considered useful to analyse the series on this basis.

Pulmonary manifestations

The radiographic pulmonary changes were evaluated on the principles established by Wurm, Reindell and Heilmeyer (1958). Stage I (Figs. 5 6) is characterized by enlarged, polycyclic hilar nodes and, sometimes, by enlargement of other mediastinal and paratracheal lymph nodes. In stage II, lymph node enlarge-



Fig 5 Pulmonary sarcoidosis at stage I. Large, polycyclic hilar lymph nodes. Tomographic radiograph of the hila region.



Fig 6 Pulmonary sarcoidosis at stage I. Large hilar lymph nodes nd normal lung parenchyma.

ment may be present but pulmonary infiltration is also demonstrable. This may vary in appearance. In stage II a (Fig. 7) the process shows primary lymphogenous retrograde extension into the lung parenchyma. The middle zones are most frequently involved, and the changes are densest in the perihilar area and slighter peripherally. In incipient cases (Fig. 8) the parenchymatous changes may be unilateral. The lung pattern is as a rule finely reticular but



Fig. 7. Pulmonary sarcoidosis at stage II a. Enlarged hilar lymph nodes with perihilary accentuated parenchymal infiltration.



Fig. 8. Pulmonary sarcoidosis at stage II. Developing parenchymal infiltration with more marked lesions in the right lung.

dense, coarsely reticular areas are also seen. The development of pulmonary infiltration is usually accompanied by regression of the lymph node enlargement. Stage II b (Fig. 9) is characterized by primary haematogenous dissemination of miliary type in the lung parenchyma. There may be either a generalized spread throughout the lungs or isolated foci. In the former case the radiographic appearance resembles that of miliary tuberculosis, with foci the size of millet grains uniformly distributed over all lung fields. Mostly the hilar node element persists irrespective of the development of pulmonary infiltration, which is in contrast to the situation in cases of lymphogenous spread. If only occasional miliary foci occur these are often larger up to the size of a pea. If these changes are localized in the apical areas, the radiographic appearance is con-



Fig. 9. Pulmonary sarcoidosis at stage II b. Miliary mottling of the parenchyma without enlargement of the hilar nodes.

fusingly like that seen in productive pulmonary tuberculosis of haematogenous origin.

Further progression of the changes in the lung parenchyma results in combination forms between stages II a and II b. Primary lymphogenous dissemination is followed by later haematogenous spread with new foci, which may increase in size and become the source of further dissemination by the lymphatics. If the new haematogenous foci do not exceed 5 mm in diameter this lymphohaematogenous combination form is termed stage II c (Fig. 10). If the foci are larger the form is termed stage II d (Fig. 11).

All changes in stages I and II may be reversible. If the foci increase in size over the limit for stage II, increased fibrotic infiltration occurs which makes



Fig. 10. Pulmonary sarcoidosis at stage II c. Somewhat enlarged hilar lymph nodes with miliary and partly nodular parenchymal infiltration (foci do not exceed 5 mm in diameter).



Fig. 11. Pulmonary sarcoidosis at stage II d. Somewhat enlarged hilar lymph nodes with miliary and nodular confluating parenchymal infiltration (foci exceed 5 mm in diameter).



Fig. 12. Pulmonary sarcoidosis at stage III a. In part confluating and exudative, in part fibrotic parenchymal lesions.



Fig. 13. Pulmonary sarcoidosis at stage III b. Final stage with severe parenchymal fibrosis.

the process irreversible. Stage III a (Fig. 12) is characterized by the presence of progressive, large confluent foci, which cause steadily increasing respiratory distress. In stage III b (Fig. 13) parenchymatous fibrosis is present, which represents a terminal stage: no further changes or exacerbations occur. The extent of the fibrosis varies with the case.

Table XIV shows the lung changes in the present series according to the classification indicated above. Owing in part to the indistinct delineation between stages II c and II d, in part to the small number of cases, these two groups were combined. The majority

Table XIV Radiographic pulmonary changes in sarcoidosis according to Wurm, Reindell and Heilmeyer

Stage	Women	Men	Total		Per cent
I	59	18	77		55
II	16	15	31	55	39
II b	5	3	8		
II c-d	10	6	16		
III	1	—	1	8	6
III b	4	3	7		

of the female patients belong to stage I (59 of 95 or 6_ per cent). Among the men, stage II is somewhat more common (24 cases) than stage I (18 patients). If only stage II is considered, perihilar lymphogenous changes are the most frequent form (II a): the miliary haematogenous form (II b) was observed in only five women (5 per cent) and three men (6.5 per cent). The series contains only eight cases at stage III. In seven of these the chest radiograph showed stationary fibrosis (III b). Tb cultures of sputum or bronchial wash were negative in all 140 cases.

In Table XV some clinical sarcoidosis series have been compiled, in which the distribution by different pulmonary stages has been indicated. In the present series the radiographic appearance of the lungs corresponded to stage I (BHL) in 55 per cent of the cases. A slightly higher figure was reported by the Swede Rudberg-Roos (196_). Considerably lower ratios have been noted in studies published in Great Britain and the U.S.A. Correspondingly the proportion of patients showing stage II was lower in the present series and that reported by Rudberg-Roos than in the British and North American series. Radiographic evidence of stage III has been found in 3–6 per cent in the series of other authors, which is in agreement with the rate of 6 per cent noted in the present series. Scadding's (1961) investigation, in which 20 per cent of the patients showed stage III constitutes an exception. This high incidence is due to the fact that a large proportion of Scadding's patients came under medical observation at a late stage. In the two North American and James' English series 6–9 per cent of the patients had normal chest radiographs. Rudberg-Roos' series includes some cases of lupus pernio without intrathoracic changes. All of the patients described by Smellie and Hoyle (1960) had lung changes, which is accounted for by the fact that the series was collected among patients with pulmonary lesions. Scadding is Head of a chest clinic, which explains why his series too consists entirely of patients with pulmonary changes.

Conclusion. The distribution of the initial pulmonary findings by different stages shows that over half the patients in the present series had lung changes corresponding to stage I (BHL alone), and 6 per cent had changes corresponding to stage III (pulmonary fibrosis). The remaining patients showed various degrees of pulmonary infiltration with or without BHL. The distribution is the same as in a Swedish series (Rudberg-Roos 1962), but as compared to British and North American reports the present series contains a larger proportion of patients with BHL alone.

Pleural changes

Exudative pleurisy was present in five patients, i.e. three women and two men. In two cases the illness started with exudative pleurisy and in two cases the pleurisy was observed in connection with an exacerbation of sarcoidosis. These four cases have previously been described in detail (Selroos 1966). The fifth case was a 27-year-old man with BHL who had been admitted to another hospital 18 months earlier on account of exudative pleurisy. At this time the chest radiograph showed a normal hilar region. The etiology of the pleurisy remained obscure. It is impossible in retrospect to decide whether any association existed between this pleurisy and the later development of sarcoidosis.

Exudative pleurisy related to sarcoidosis is a rare event. Mayock et al. (1963) who surveyed the findings in five reported sarcoidosis series, noted pleural effusion in seven (1.5 per cent) of the total number of 475 patients. The previously published cases of sarcoidosis showing exudative pleurisy have been reviewed by the present writer (Selroos 1966). In this study the frequency was found to be 2.8 per cent, or

Table XV Percentual distribution of patients by pulmonary stage in some clinical series of sarcoidosis.

	No. of patients	Stage I	Stage II	Stage III	Normal chest radiograph
England:					
James (1956)	150	39	49	3	9
Smellie and Hoyle (1960)	125	38	57	6	–
Scadding (1961)	136	23	57	20	–
Sweden.					
Rudberg-Roos (1962)	296	58	36	5	1
U S A					
Israel and Sones (1958)	160	34	60)		6
Siltzbach (1967)	311	43	49)		8
The present series	140	55	39	6	–

) An unknow number f patients showed fibrotic changes, but the number of cases at stage III is not separately indicated.

)

somewhat higher than the previously reported figures, but the small number of cases does not allow of any confident estimation.

Spontaneous pneumothorax was not observed in the present series, but it has been described, in particular in patients with chronic pulmonary fibrosis. Specific changes have rarely been demonstrable the pneumothorax has been caused by leakage from emphysematous bullae (Scadding 1967) Since the present series contains only a few patients with pulmonary fibrosis and emphysema, it is understandable that pneumothorax did not occur

Bronchial sarcoidosis

Ninety patients (64 per cent) were bronchoscopied. Only two showed evident macroscopic mucosal changes. In one case a nodular pale infiltration in the bronchial mucosa was observed. The other patient showed obvious narrowing of the apical segmental branch of the right lower lung lobe. In both cases the diagnosis was confirmed by biopsy The radiographic finding corresponded to stage II in both patients.

As regards the remaining 88 cases, an entirely normal bronchial tree was seen in 40 while in 48 cases the smooth mucosa showed reddening or the blood vessels were more conspicuous than usual. Biopsy was performed in 29 cases in the former group and in all 48 in the latter The groups are separately discussed below

Table XVI shows the results of 56 biopsies in 29 patients with entirely normal bronchoscopy findings. The biopsy was positive in four cases of 16 (25 per cent) at stage I and in eight of 12 (67 per cent) at stage II This group contains only one patient at stage III of two biopsy specimens, one showed sarcoid granuloma. The results do not seem to depend on the site of the biopsy The ratio of positive results is not significantly higher for any of the six biopsy sites in cases with pulmonary changes at the same stage. It is noteworthy that no biopsy of the carina was positive, but only five such biopsies were performed and four of these on patients at stage I. The importance of performing multiple biopsies is obvious. In the present series an average of two biopsy specimens per patient were taken. In two cases only (one at stage I the other at stage II) were characteristic granulomas seen in both specimens. Otherwise the finding was positive in only one of two or three specimens obtained. In the 16 cases in which the finding was positive, two biopsies had been performed in 13 cases and only one in three cases.

When all biopsied patients with a macroscopically normal mucosa are considered and the pulmonary stage is disregarded, the finding was positive in over one fourth (15 of 56). On comparison of the different pulmonary stages it is found that patients at stage II had positive biopsies twice as often as those at stage I

Table XVII shows the bronchial biopsy findings in those 48 cases in which slight unspecific changes were observed on inspection. Six patients of 24 at stage I (25 per cent) and 17 of 22 at stage II (77 per cent) had positive biopsies. The finding was also positive in one of two patients showing pulmonary changes at stage III

As may be seen in the table, none of the nine carina biopsies performed in cases at stage I gave positive findings. Of all 47 biopsy specimens taken at this stage, only six (13 per cent) showed sarcoid granulomas. The findings were more often positive in the group with stage II pulmonary changes, or in 26 biopsies of 42 (62 per cent). The distribution of positive findings over different sites is strikingly uniform, as estimated in relation to the number of biopsies performed on the sites in question.

When, among the patients with lung changes at stage I the group with an entirely normal mucosa is compared to the group showing slight unspecific changes, it is found that in both groups 25 per cent had positive biopsies. As regards those with pulmonary changes at stage II the results were more often positive in the group in which the mucosa showed slight unspecific changes (77 per cent) than in the group with a normal mucosa (67 per cent), but the difference is not statistically significant On the other hand, a statistically significant difference was

Table XVI. Results of biopsy of bronchial mucosa at different pulmonary stages in patients with normal gross findings.

Stage	No. of pat	No. of pat. with pos. biopsies	Positive in per cent	Site of biopsy — No. of positive/no. of performed biopsies: Carina	Right upper lobe	Right median lobe	Right 6th	Left upper lobe	Left 6	Total	Per cent
I	16	4	25	0,4	2/12	1/2	2/10	0/2	0/0	5/30	17
II	12	8	67	0,1	3/9	0/1	4/9	1/3	1/1	9/24	38
III	1	1	(100)	0/0	1/1	0/0	0/1	0/0	0/0	1/2	(50)
Total	29	13	45	0/5	6/22	1/3	6/20	1/5	1/1	15/56	27

Table XVII. Results of biopsy of bronchial mucosa at different pulmonary stages in patients with reddening or unspecific macroscopic changes.

Stage	No. of patients	N of pat. with pos. biopsies	Positive in per cent	Site of biopsy No of positive/no. f performed biopsies. Carina	Right upper lobe	Right median lobe	Right "6"	Left upper lobe	Left 6"	Total	Per cent
I	24	6	25	0/9	2/14	0/0	3/17	0/4	1/3	6/47	13
II	22	17	77	4/9	6/10	2/3	8/14	3/3	3/3	6/42	62
III	2	1	(50)	0/0	0/0	0/0	1/1	0/1	0/1	1/3	(33)
Total	48	4	50	4/18	8/24	2/3	12/32	3/8	4/7	33/92	36

observed between the rate of positive findings in cases at stage II and cases at stage I, irrespective of the appearance of the mucosa. In the stage I group of patients, 11 of 77 (14 per cent) biopsies were positive against 35 of 66 (53 per cent) in the stage II group.

Specific macroscopic changes of the bronchial mucosa are rare in sarcoidosis. By contrast, unspecific changes such as thickening, reddening and more conspicuous blood vessels are relatively frequent. Such features may be seen at stage I and are considerably more common in the presence of pulmonary infiltration (stage II) and relatively rare at stage III when the mucosa shows incipient atrophy. The first to report these observations were Turiaf and Brun (1955) who also showed that typical granulomatous tissue may be encountered in a macroscopically normal mucosa as well. Considering that the macroscopic changes are unspecific, it is not surprising that the reported ratios vary. In a series of 71 cases Turiaf (1964) noted unspecific changes in 56 and specific changes in three, while 12 patients had normal mucosa. Liot et al. (1963) reported thickening and reddening of the mucosa in 117 of 123 cases (95 per cent). Macroscopic findings slightly deviating from the normal were observed by Siltzbach and Cahn (1964) in 22 of 49 patients (45 per cent). An extensive survey of the bronchial changes in sarcoidosis has been published by Huzly et al. (1963).

The results of mucosal biopsy have varied depending on whether the bronchial mucosa was normal in appearance on bronchoscopy or showed gross (though mainly unspecific) changes. Siltzbach and Cahn (1964) reported 82 per cent positive specimens (18/22) in cases showing macroscopic involvement and 44 per cent (12/27) when the mucosa was grossly normal. By contrast, Turiaf (1964) found that the rate of positive findings was the same irrespective of the appearance of the mucosa. In a group with macroscopically normal mucosa he had six positive biopsies among 12 performed (50 per cent), and in a group with unspecific macroscopic changes 26 biopsies were positive among 56 performed (46 per cent).

The rate of positive bronchial mucosal biopsies has also differed as related to the different stages of lung changes. Higher figures have usually been noted in patients showing pulmonary infiltration.

At *stage I* (BHL alone) highly different results have been obtained. In nine cases Carlens (1964) reported no positive biopsy findings, although three specimens were taken in each case. Ståhle (1964) reported positive findings in 15 per cent (4/27). On the other hand, Schiessle et al. (1961) found bronchial biopsies positive in 45 per cent (13/29), Liot et al. (1963) in 54 per cent (34/63) Siltzbach and Cahn (1964) in 40 per cent (6/15), Turiaf (1964) in 41 per cent (9/22), and Kessler and Behrend (1966) in 51 per cent (19/37).

At *stage II* bronchial biopsies have been positive more often than at stage I. Positive specimens were obtained by Schiessle et al. (1961) in 75 per cent (39/52) and in a later study (1963) in 78 per cent (62/126) by Carlens (1964) in 17 per cent of cases (6/35), by Ståhle (1964) in 44 per cent (12/27), by Turiaf (1964) in 52 per cent (24/46), by Siltzbach and Cahn (1964) in 70 per cent (24/34) and by Kessler and Behrend (1966) in 55 per cent (39/71)

The number of reported cases at *stage III* is small. Turiaf (1964) observed granulomatous tissue in two cases out of three in which bronchial mucosal biopsy was performed. Ståhle (1964) reported similar findings in three cases of 19 (17 per cent) and Carlens (1964) in five cases of 12 (42 per cent). Kessler and Behrend (1966) obtained positive specimens in 34.5 per cent (10/29). A larger series was presented by Schiessle et al. (1963), who reported positive bronchial biopsies in 50 per cent of 60 investigated cases of pulmonary fibrosis.

In the present series the gross bronchoscopy finding was normal in 40 patients (45 per cent) which is the same as in the series of Siltzbach and Cahn. In the various French series, on the other hand, considerably higher rates of unspecific macroscopic changes have been noted.

When the bronchial mucosa was normal in appear-

ance, positive biopsy specimens were obtained in 45 per cent of cases in the present study In the group showing slight unspecific changes the corresponding figure was 50 per cent The difference is slight, which is in agreement with the results reported by Turiaf (1964) Siltzbach and Cahn (1964), on the other hand, obtained positive specimens in a much larger proportion of cases with macroscopically normal mucosa (82 per cent)

In no previously reported series has the result of bronchial mucosal biopsy been related to both pulmonary stage and gross findings. Since in the present series the results are approximately the same in the groups with normal mucosa and with slight unspecific changes, these have been united in the following analysis.

The biopsy finding was positive in 25 per cent of the present cases at stage I. This is a considerably higher ratio than in the two Swedish investigations referred to above (Carlens 1964 Ståhle 1964) but lower than in the series of Siltzbach and Cahn (1964) and in the German (Schiessle et al. 1961 Kessler and Behrend 1966) and French series (Liot et al. 1963 Turiaf 1964). The cause of this remains obscure. Obviously it has nothing to do with the number of biopsy specimens taken, since Carlens took three specimens in each case and nonetheless reported the lowest ratio of those reviewed. Perhaps the relative smallness of the series affords an explanation. In the present series bronchial biopsies were found positive in 70 per cent of the cases at stage II, which is in agreement with the results reported by Schiessle et al. (1961 1963) and Siltzbach and Cahn (1964). On the other hand, the ratio of positive findings was definitely lower in the above-mentioned Swedish and French series and in the study of the Germans Kessler and Behrend (1966) As regards stage III, in the present series only three biopsies were performed of which two were positive. Since the series reviewed also contain only a few cases at this stage, no confident statement can be made concerning the frequency of positive bronchial biopsy findings. An exception is formed by the study of Schiessle et al. (1963) in which 30 biopsies of 60 performed were positive.

On comparison of the biopsy results from different sites of the bronchial tree it is found that in the present series the ratio of positive findings was lowest in the carina biopsies. As regards the other more distal sites, the proportion of positive findings was greater and more or less the same for all. This is in agreement with the results of Schiessle et al. (1961) in a study of 33 bronchial mucosal biopsies performed in 126 cases of sarcoidosis in which for the sake of comparison specimens were taken from five different peripheral sites

Conclusion Specific macroscopic mucosal changes are rarely seen on bronchoscopy On the other hand, in the present series unspecific changes were frequent findings. The results of mucosal biopsy showed no relationship with the gross findings. The importance of multiple specimens was clear since all specimens obtained were seldom positive. The ratio of positive biopsies was highest in the group of patients with pulmonary infiltration, but even in those with BHL alone the proportion of positive biopsy findings was as high as 25 per cent. The cases showing stationary fibrosis were too few to allow of confident conclusions. The results agree fairly well with those reported in a North American (Siltzbach and Cahn 1964) and a German (Kessler and Behrend 1966) series, but the ratio of positive biopsies in higher than in two Swedish investigations (Carlens 1964 Ståhle 1964), which comprised fewer patients, and somewhat lower than in two French studies (Liot et al. 1963 Turiaf 1964), and in an earlier German series (Schiessle et al. 1963).

Erythema nodosum

Erythema nodosum (EN) was the initial symptom of sarcoidosis in 29 cases, as reported on p 26. In addition, EN was observed in another 13 patients, although these presented with some other symptom. EN was thus noted in a total of 42 patients (30 per cent) of whom 35 were female and seven male. This implies that EN occurred in 37 per cent of the female and 16 per cent of the male cases. As regards the distribution by different stages of pulmonary involvement, of the 35 women 33 had lung changes corresponding to stage I and the remaining two had changes at stage II. Of the total number of 59 female patients with pulmonary changes at stage I, 56 per cent had concomitant EN Of 31 patients at stage II only two (5.5 per cent) showed EN Of the seven men with EN three had lung changes at stage I (17 per cent of the men at stage I) and four had changes at stage II (17 per cent of the men at stage II)

The age distribution of the patients showing EN may be seen in Table XVIII The majority were 30–39 years old. When the total number of patients in the different age groups is considered, the ratio of EN among the female patients is found to be highest in the age group 21–29 years (62 per cent) and then declines with increasing age. As regards the female groups under 20 and over 60 years old and all male groups, the number of patients is too small to allow of confident estimations of the frequency of EN.

Although occasional cases of EN concomitant with sarcoidosis had previously been described, it was principally *Löfgren* (1953 a) who drew attention

Table XVIII. Age and sex distribution of 42 sarcoidosis patients with erythema nodosum. In each age group the number of erythema nodosum patients is indicated in relation to the total number of patients in the same age group.

Age group	–19	20–29	30–39	40–49	50–59	60–	Total
Women	1/1	8/13	10/25	10/30	4/22	2/4	35/95
Men	0/0	1/15	5/18	1/9	0/2	0/1	7/45
Total	1/1	9/28	15/43	11/39	4/24	2/5	42/140

to the fact that EN is frequently associated with acute-subacute sarcoidosis. In a series consisting of 212 patients with BHL he observed EN in 107 of 161 women (67 per cent) and in six of 51 men (12 per cent). Among the 113 patients with BHL and EN 10 also had pulmonary infiltrations. Of the female patients 85 (80 per cent) were under 40 years of age the ratio of EN was highest in the age group 25–29 years (34 cases, 32 per cent). When classified into 10-year groups 43 patients belonged to the 20–29 group and 42 cases to the 30–39 age group.

In Putkonen's (1966) series of 85 patients with subacute sarcoidosis, 42 (49 per cent) had EN. This symptom was noted in 62 per cent of the female patients and 22 per cent of the men.

In series also containing cases other than acute-subacute sarcoidosis the ratio of EN has of course been lower. James (1956) observed EN in 34 patients of 150 (23 per cent), Hedvall (1960) in 40 patients of 142 (28 per cent), Smellie and Hoyle (1960) in 16 cases of 125 (13 per cent) Rudberg-Roos (1962) in 87 patients of 296 (29 per cent) and Lebacq (1964) in 25 of 100 (25 per cent). Wurm et al. (1965) noted EN in 218 cases of 2,177 (10 per cent).

As compared to the above-mentioned Scandinavian, British, German and Belgian studies, the frequency of EN seems to be considerably lower in series from the U.S.A. Israel and Sones (1958) observed EN in three patients of 160 (2 per cent), Mayock et al. (1963) in four of 145 (3 per cent). Both these series were predominantly negro. Siltzbach (1967a) found EN in 33 of 311 patients (11 per cent) in a series comprising more whites and Puerto Ricans than negroes. EN in association with sarcoidosis is also rare in Japan. Nobechi (1964) found only one case among 282 patients with sarcoidosis.

On comparison with other European series it is found that the frequency of EN in the present study is about the same as in non-selected Scandinavian series. It is somewhat higher than the figures indicated in British reports and one Belgian investigation and considerably higher than the frequency in the German series of Wurm et al.

Of James (1961a) 126 patients with EN and sarcoidosis 93 (74 per cent) were female. Of these, 49 per cent were aged 20–29 years and 26 per cent were aged 30–39 years. In Löfgren's (1953 a) series 95 per cent of the patients with EN were female. In this respect the present series occupies an intermediate position, 83 per cent of the cases of EN being female. A female predominance is typical of all series. In regard to the age distribution it is found that the 20–29 group is the largest in both Löfgren's and James' series, while in the present series the 30–39 group is the largest. It is also noteworthy that the number of female patients with EN is the same in the 40–49 and 30–39 groups. This age distribution is accounted for by the fact that in the present series of sarcoidosis the total number of cases is small in the 20–29 group. If the number of patients with EN is considered in relation to the total number of cases in the respective age groups, the ratio is found to be highest in the 20–29 group and to decrease with increasing age in this series also. Thus, the difference does not seem to be due to a later appearance of EN but to the fact that in Finland sarcoidosis as such seems to commence at a later age.

The most frequent chest radiographic finding associated with EN is BHL. In addition, pulmonary infiltration was reported by Löfgren (1953 a) in 9 per cent of cases and by James (1961a) in 6 per cent. In the present series which, however comprises fewer cases of EN pulmonary infiltration was observed in 14 per cent of the cases (6/42). It is noteworthy that four of these six patients were male.

Conclusion. In the present series the ratio of EN is the same as in other non-selected Scandinavian series though higher than in some other European and in North American studies. EN was observed in women more often than in men (4:1) and was percentually more common in the younger age groups. The absolute number of patients with EN was highest, however in the 30–39 group and the female patients with EN were equally numerous in the 40–49 group as in the 30–39 group. It thus appears that sarcoidosis commenced at a later age in the present patients than in the series previously described.

Ocular manifestations

A total of 69 patients were examined by an ophthalmologist. Five of these had ocular manifestations on admission (Table XI). Changes considered as

being due to sarcoidosis were observed in 14 cases (nine female, five male) (20 per cent). Nine patients had uveitis, and three of these also showed secondary glaucoma, while one showed slight retinal changes possibly caused by sarcoidosis. Two patients exhibited changes of the conjunctiva (conjunctivitis follicularis). In one of these cases a biopsy specimen revealed productive granulomas of sarcoid type in the other no biopsy was performed. One patient only showed changes of the eyegrounds considered as specific.

In five cases acute uveitis and pulmonary lesions were detected at the same time. One of these patients also showed retinal changes. In one symptom-free patient with changes of the eyeground and two with conjunctival involvement the diagnosis of sarcoidosis was established by ophthalmological examination within one month from the observation of pulmonary lesions. The remaining six patients had longer histories:

A 64-year-old woman showed exudative, in part fibrotic in part confluent pulmonary infiltration due to sarcoidosis. Four years earlier she had uveitis and enlarged hilar lymph nodes, but the disease was not then correctly diagnosed.

A 51-year-old woman had acute uveitis and pulmonary infiltration of unknown character seven years before admission to hospital. When sarcoidosis was diagnosed, she showed secondary glaucoma, skin manifestations and pulmonary lesions.

A 9-year-old woman had uveitis two and three years before sarcoidosis was diagnosed. She sought medical advice because of EN and hilar node enlargement was detected. Signs of chronic uveitis were then observed, which were considered by the ophthalmologist as due to sarcoidosis.

A 41-year-old man had an attack of renal colic four years, and recurrent iritis one year before admission to hospital. He was admitted on account of recurrent attacks of renal colic. Hypercalcaemia, hypercalciuria, uveitis and enlarged hilar nodes were then observed.

A 40-year-old woman had bilateral uveitis two years before she developed renal calculi, which were operatively removed. A biopsy specimen of the kidney taken at the same time showed sarcoid granulomas, and the Kveim test was positive. Four years later a chest radiograph still showed no changes, but after another year pulmonary infiltration was observed, which soon became fibrotic.

A 30-year-old man developed acute uveitis, and at the same time pulmonary changes considered as tuberculous were observed. The patient was therefore admitted to a sanatorium. Three years later when he had moved to the district covered by this study he was summoned to investigation and the diagnosis of sarcoidosis was made.

It is noteworthy that in three cases no pulmonary lesions were present at the time when ocular manifestations first occurred. In the remaining cases pulmonary and ocular manifestations were observed at the same time.

Concomitant involvement of the parotid gland (Heerfordt's disease) did not occur nor keratoconjunctivitis sicca. Although hypercalcaemia was noticed in four patients with ocular sarcoidosis, no calcium deposits were observed in the cornea or conjunctiva.

Ever since it was shown by Bruins Slot (1936) that Heerfordt's disease is a manifestation of sarcoidosis, great attention has been paid to the occurrence of ocular symptoms in sarcoidosis patients. The most frequent ocular manifestation is uveitis. Others include infiltration of the lacrymal glands, keratoconjunctivitis sicca and changes in the cornea and bulbar conjunctiva resulting from hypercalcaemia (Scadding 1967). The frequency figures for ocular manifestations have a wide range in clinical series of sarcoidosis. This is due in part to the different ways in which the series have been collected, and in part to the fact that the ratios depend on whether the patients have been examined by an ophthalmologist. It is understandable that higher ratios of ocular manifestations are reported by authors co-operating closely with an opthalmological clinic or with ophthalmologists. Even though uveitis is the most common ocular manifestation in sarcoidosis, uveitis is due to sarcoidosis in only _ per cent of all cases (Perkins 1958).

The literature concerning ocular sarcoidosis published before 1950 has been reviewed by Longcope and Freiman (1952). Later surveys have been written by James (1959 a) and Scadding (1967).

The frequency figures for ocular manifestations have ranged from 8 per cent (Ricker and Clark 1949) to the very high ratio of 64 per cent in the 7? Baltimore patients described by Longcope and Freiman (1952). In this series the majority were negroes, and it is noteworthy that ocular sarcoidosis has been more often observed in this race than in whites. The figures indicated in English and Scandinavian series have been of quite a different magnitude. James (1956) observed ocular manifestations in 2? per cent of 150 patients, and Scadding (1967) reported uveitis in 14 per cent of 275 patients. Rudberg-Roos (1962) noticed uveitis in __ patients of 204 (11 per cent) and Putkonen (1966) in 1? patients of 85 (15 per cent) with subacute sarcoidosis. Löfgren (1953 b) observed uveitis in 13 cases of _ (6 per cent).

In the present series uveitis was the most frequent ocular manifestation, just as in other reports. Fourteen patients showed ocular disease. This makes 10 per cent of the whole series, but 20 per cent of those patients who were examined by an ophthalmologist irrespective of their symptoms. This shows the importance of including ophthalmological examination among the routine procedures. The ratio is in

agreement with the figures reported in earlier English and Scandinavian clinical series, collected in the same way as the present one.

Skin manifestations

Skin manifestations of two different kinds were observed in the present patients: acute cicatricial reactions and chronic nodular skin sarcoidosis.

In five patients (three men and two women) healed, quiescent scars of old standing suddenly became swollen, hypertrophic and tender in connection with the development of acute sarcoidosis. Considering that all patients in the present series were thoroughly investigated for cicatricial reactions, the frequency is not high. In the above-mentioned five cases a biopsy specimen of the scar tissue was taken, a granulomatous tissue reaction of sarcoid type was found in four.

Nodular skin sarcoidosis was seen in four patients. In all of these a biopsy specimen showed features consistent with the diagnosis of sarcoidosis. In one case the diagnosis was made on the basis of pulmonary fibrosis observed when the patient sought medical advice on account of his skin lesions. In the remaining three cases skin lesions developed during the time of observation. One patient developed skin sarcoidosis and concomitant splenomegaly three years after an acute attack of EN and BHL. In two cases skin sarcoidosis was observed seven years after the onset of uveitis and pulmonary manifestations.

Total alopecia occurred in one case, but no definite relationship with the sarcoidosis could be established.

As already mentioned in the introductory chapter the history of sarcoidosis begins with the description of skin manifestations. Extensive surveys of the different forms of skin lesions have been published by Pautrier (1940), James (1959 b) and Ehring (1965). Various series differ widely in regard to the ratio of skin manifestations depending on the way in which the cases have been collected. In their Boston series Longcope and Freiman (1952) observed skin sarcoidosis in 63 per cent of the patients, many of whom had been remitted by dermatologists. In their Baltimore series skin lesions occurred in 44 per cent. Putkonen (1966) noticed skin sarcoidosis in 23.5 per cent of 85 patients with subacute sarcoidosis admitted to a dermatological clinic, while Löfgren (1953 b) observed skin lesions in only 5 per cent of his 212 patients with BHL. In North American series which are predominantly negro the ratio of skin sarcoidosis is higher than in series consisting of whites (Longcope and Freiman 1952, Sones and Israel 1960). In a series of 211 patients, 87 per cent of whom were negro Sones and Israel noted skin sarcoidosis in 29 per cent of the negroes and 11 per cent of the whites.

In series from the U.S.A., which as a rule consist of chronic cases to a greater extent than European series, skin manifestations have been observed in over 30 per cent of the patients (Mayock et al 1963). Siltzbach (1967 a), who described a series consisting to 78 per cent of subacute cases, noticed skin lesions in only 19 per cent. In England, James (1956) observed skin sarcoidosis in 29 of 150 patients (19 per cent) and Smellie and Hoyle (1960) in 17 of 125 (14 per cent). In the Swedish series reported by Rudberg-Roos (1962) skin lesions were found in 10 per cent of the verified cases of sarcoidosis.

In the present series cicatricial reaction of scars was seen in five cases (3.5 per cent), which is somewhat more than in Löfgren's (1953 b) series. He observed a cicatricial reaction in two patients of 212 showing BHL (1 per cent). On the other hand, the rate of skin lesions is considerably lower in the present series than in Putkonen's (1966) series of subacute sarcoidosis, in which 16 patients of 85 or 19 per cent, showed skin manifestations.

Four patients in the present series showed nodular skin sarcoidosis. Thus, specific skin lesions were seen in nine patients (6 per cent) which is a low ratio as compared to the figures given in the above-mentioned reports.

Changes of the bone

Radiographs of the hands and feet were taken in 85 cases. Three patients (3.5 per cent of those examined) showed cystic formations of the same type as have previously been described in sarcoidosis. In one of these cases the initial manifestation was a swollen and painful thumb showing a typical cystic formation. The other two patients were asymptomatic as far as the bone was concerned. One of them also had skin lesions.

In clinical series of sarcoidosis the ratios of skeletal involvement vary just as do the frequency figures for other organ manifestations, depending on the methods of investigation and the way in which the series have been collected. Changes of the bone are known to be rare in acute sarcoidosis and to occur more often in chronic cases, particularly in those also showing skin manifestations. In North American series the frequency of skeletal lesions ranges between 16 and 26 per cent (Mayock et al. 1963). Siltzbach (1967 a) observed such lesions in 9 per cent of a series predominantly consisting of subacute cases. James (1956) noticed skeletal changes in eight out of 150 patients (5 per cent) and Lofgren (1953 b) in only two patients of 212 showing BHL, but not all his

patients had been investigated for changes of the bone. Rudberg-Roos (196.), whose series resembles the present one in regard to composition, observed skeletal manifestations in three patients of 178 examined (1.7 per cent).

The present observations confirm the results of other authors who have shown that changes of the bone are rare in the acute-subacute form of sarcoidosis, which is predominant in Scandinavia and England.

Renal manifestations

Renal changes of three kinds were observed in the present series: 1) interstitial, non-granulomatous tissue reaction in acute sarcoidosis, 2) sarcoid granulomas in the renal tissue and 3) nephrocalcinosis resulting from hypercalcaemia and hypercalciuria.

Interstitial nephritis. A male patient showing pulmonary changes of stage I had proteinuria and glycosuria, but his renal function was normal. No disturbance of the calcium metabolism could be demonstrated. Percutaneous renal biopsy revealed accumulation of mononuclear cells in the interstitial tissue, a finding which is indicative of acute interstitial nephritis. The glomeruli were entirely intact, the tubuli were in part oedematous.

Granulomas in the renal tissue were observed in three patients. In one case the disease commenced with an attack of renal colic. A calculus was operatively removed, and a biopsy specimen of the kidney taken at the same time showed epithelioid cell granulomas of sarcoid type. The patient's renal function was normal. Neither hypercalcaemia nor hypercalciuria was observed.

Granulomas in percutaneous renal biopsy specimens were also found in another two cases. One of these patients had a history of renal colic, but renal function and the serum and urinary calcium values were normal. These values were also normal in the other patient. Neither showed abnormal urinary sediment or radiological signs of nephrocalcinosis. Both patients had pulmonary lesions corresponding to stage I.

Normal renal biopsy specimens showing no signs of interstitial nephritis or granuloma were obtained in eight cases in which the serum and urinary calcium values and renal function were normal. One of these patients showed proteinuria in connection with an attack of fever associated with EN. A normal renal biopsy specimen was also obtained in a case of hypercalcaemia and slight renal failure without radiologically evident nephrocalcinosis.

Nephrocalcinosis was noted in three patients.

Two years after sarcoidosis had been diagnosed, a 34-year-old woman developed hypercalcaemia, hypercalciuria and slight renal failure (serum creatinine 1.6–... mg/100 ml). Nephrocalcinosis was demonstrated both radiologically and by renal biopsy. The patient was treated with glucocorticoids for 28 months. The calcium values and renal function returned to normal and nephrocalcinosis was no longer demonstrable. A renal biopsy specimen obtained eight years later was normal.

A 59-year-old woman had recurrent attacks of renal colic seven years after the diagnosis of sarcoidosis had been made on the basis of pulmonary changes and acute iritis. Hypercalcaemia, slight renal failure and radiologically evident nephrocalcinosis were observed. In spite of glucocorticoid therapy her condition was unchanged five years later at the time of writing.

A 41-year-old man fell ill with an attack of renal colic. Sarcoidosis was diagnosed on account of the pulmonary changes and iritis simultaneously observed. In addition, a lymph node biopsy was positive. Renal function was normal and so were the serum and urinary calcium values. Five years later hypercalcaemia, hypercalciuria, radiologically evident nephrocalcinosis, renal failure (serum creatinine 2.0–2.3 mg/100 ml) and severe changes in a renal biopsy specimen were noted.

Renal calculi. In addition to those four cases described above in which renal calculi developed (two cases of nephrocalcinosis and two cases of sarcoid granulomas in the renal tissue) two patients presented with renal colic. The ratio of renal calculi in the present series is 4.2 per cent.

In most reports on renal involvement associated with sarcoidosis, the lesions described have been due to nephrocalcinosis, but occasional cases of various other disturbances have been reported. In a survey of the renal changes in sarcoidosis, Otto (1963) stated that 19 per cent of all patients with this disease develop some form of renal disturbances during the course of the illness, and that 2.5 per cent die of renal failure. He found the following renal manifestations described in the literature: a) sarcoid granulomas in the renal tissue, b) renal calculi, c) compression of the ureter due to the presence of sarcoidosis lesions in the periureteral tissue, d) nephritis with hyalinosis and perivascular changes, e) glomerulitis with thickening of Bowman's capsule, f) interstitial nephritis in chronic sarcoidosis with resultant secondary nephrocirrhosis and renal failure, g) nephrotic syndrome, h) nephrocalcinosis, i) hepato-renal syndrome in severe sarcoidosis of the liver and j) concurrence of renal sarcoidosis and other renal diseases.

To the best of the writer's knowledge, reversible acute interstitial nephritis associated with acute sarcoidosis, as was seen in one of the present cases, has not previously been described.

Owing to the scantiness of data, it is difficult to assess the frequency of granulomatous changes in

the renal parenchyma in sarcoidosis. At autopsy Ricker and Clark (1949) found renal sarcoidosis in five cases out of 22 showing disseminated lesions, and Longcope and Freiman (1952) reported the same finding in four cases out of 23. In percutaneous renal biopsy specimens Löfgren et al. (1957) found sarcoid granulomas in one patient out of 10 without hypercalcaemia and in three patients out of six with hypercalcaemia.

In the presence of normal renal function and normal findings in the urinary sediment, renal biopsy has not been performed to any considerable extent in patients with sarcoidosis. In the present series percutaneous renal biopsy was performed on 12 patients. Granulomatous changes were found in two. In both cases renal function and the urinary sediment were normal, neither patient showed hypercalcaemia or hypercalciuria, and the pulmonary findings corresponded to stage I. In such cases a larger series of biopsies is required for conclusions to be drawn as to whether the formation of granulomas in the renal parenchyma in acute-subacute sarcoidosis is a spontaneously reversible process resembling the not infrequent granulomatous changes in the liver.

Sarcoid granulomas in the renal parenchyma without concomitant nephrocalcinosis rarely leads to renal failure. Scadding (1967) found only six such cases in the literature, and not all of these were definite.

Nephrocalcinosis and renal failure were not infrequently seen during the period when sarcoidosis was treated by vitamin D therapy. However protracted hypercalcaemia and hypercalciuria may lead to nephrocalcinosis even without the administration of vitamin D and this often results in impaired renal function. This is the most frequent finding in the cases of renal involvement described (Otto 1963 Scadding 1967). Löfgren et al. (1957) found that six patients who showed or had shown hypercalcaemia over 12 mg/100 ml also had decreased p-aminohippuric acid clearance and somewhat decreased creatinine and inulin clearance. NPN was elevated in three cases. The biopsy specimens showed calcium precipitation in the interstitium and tubuli, hyalinization of Bowman's capsule and, in three cases, granulomatous changes in the interstitium. In 10 patients without hypercalcaemia the renal function was not appreciably disturbed, and no calcium precipitation was seen.

As compared to the series of Löfgren et al. (1957) the results in the present study were not equally definite. Thirteen patients had serum calcium values over 11 mg/100 ml, and 10 patients had a calcium excretion in the urine exceeding 300 mg/24 h, but of these patients only three showed nephrocalcinosis and impaired renal function. However since biopsy was performed in only one of the remaining cases of hypercalcaemia, it is possible that calcium precipitation was present although it was not radiologically evident.

Of special interest is the case of nephrocalcinosis, described in the foregoing in which both this condition and the resulting renal failure proved to be reversible with glucocorticoid treatment. Another similar case was observed later when the collection of the present series had been completed.

Conclusion Renal changes of various types are seen in sarcoidosis. The frequency of the different manifestations cannot be estimated owing to the scantiness of available data. However both granulomatous changes and nephrocalcinosis occur more frequently in chronic, disseminated sarcoidosis than in acute cases. Certain findings in the present series seem to suggest that both interstitial and granulomatous lesions may also occur in the early stage of sarcoidosis.

Splenomegaly

Two of the present patients showed splenomegaly In a 28-year-old man the illness started with parotid gland enlargement, peripheral facial paresis and considerable enlargement of the cervical lymph nodes. A chest radiograph showed enlarged hilar nodes. The patient recovered during glucocorticoid treatment. Two years later he had a recurrence with enlargement of cervical lymph nodes and concomitant splenomegaly The other patient was a 45-year old woman who developed acute sarcoidosis with EN and BHL. Three years later pulmonary lesions corresponding to stage II, skin sarcoidosis and splenomegaly were noted. In both these cases a decrease in size of the spleen was obtained by glucocorticoid treatment.

In autopsy series of sarcoidosis, varying ratios of involvement of the spleen have been reported. According to the data collected from the literature by Longcope and Freiman (1952), sarcoidosis of the spleen had been detected in 31 of 40 cases examined post mortem. These authors themselves found sarcoidosis in the spleen in 10 among 26 autopsied cases. The frequency figures for palpable spleen have also varied greatly This finding was reported by Ricker and Clark (1949) in 16 cases of 195 (8 per cent) and by Longcope and Freiman (1952) in 22 of 52 (42 per cent) of their Boston patients. In Scadding's series (1967) the spleen was palpable in 11 per cent of 775 cases. Siltzbach (1967a), whose series in many respects differs from other North American ones and shows a resemblance to European series, observed a palpable spleen in 18 per cent of 311

patients. In Scandinavian series enlargement of the spleen has been infrequent. Nitter (1953) found five cases of splenomegaly among 90 Danish patients, and Rudberg-Roos (1962) reported enlargement of the liver or spleen in six patients of 296.

Splenomegaly was an infrequent finding in the present series. The ratio was approximately the same as in a similar Swedish series (Rudberg-Roos 1962), but lower than in the other reports cited above.

The Kveim reaction

Owing to the lack of antigen, Kveim's test could not be performed on patients investigated during the period 1959–1962. In 1963 it became possible to include this test among the routine examinations by the courtecy of Professor Louis E. Siltzbach, New York, who kindly made his reference antigen (Chase-Siltzbach, Type I) available. This antigen was used until the beginning of 1967. Biopsy specimens were taken from the test papules and the histopathological reaction was evaluated by the writer, the respective hospital pathologists and Siltzbach. Later in 1967 an Australian antigen was also used, which was kindly made available by Dr T. H. Hurley, Melbourne. These biopsy specimens of test papules were also evaluated by the writer and the local pathologists. Since comparative studies on Siltzbach's and Hurley's antigens (Hurley and Bartholomeusz 1967) have shown a remarkable agreement, the results obtained with the two antigens are not discussed separately.

Kveim's test was performed in 96 cases (69 per cent of the series). The results are shown in Table XIX. The test was performed on 23 patients with pulmonary changes of stage I and EN. The result was positive in 2_ (96 per cent). The Kveim-negative patient was first treated at another hospital. At this time BHL was present in addition to EN. A definite diagnosis was not made, however, and the patient was therefore investigated again four months later. The hilar node enlargement had then almost disappeared, and the Kveim test was negative. In 33 cases Kveim's test was performed on patients showing pulmonary lesions of stage I without EN. The result was positive in 29 cases (87 per cent). The four Kveim-negative patients were all symptom-free when they were summoned to investigation on account of hilar node enlargement detected at compulsory mass radiographic survey.

Of 37 patients at stage II, 25 (68 per cent) reacted positively to the Kveim test. Of the 12 Kveim-negative patients seven were symptom-free when they were investigated for sarcoidosis. In these cases the duration of illness could not be established. Five of the patients who reacted negatively had had subjective symptoms for respectively two months, 10 months, one year, one year and at least five years. Three of these patients were over 50 years of age, one was 31 and one 38 at the time of the diagnosis. In one of the last-mentioned cases the test was performed during glucocorticoid treatment.

Three patients with pulmonary changes corresponding to stage III were Kveim tested. The result was negative in all. Two of these patients had shown stationary lung lesions for several years. The third patient had a four year history which started with uveitis, followed by secondary glaucoma.

In the group of 44 patients on whom Kveim's test was not performed during the period covered by the present study, three patients showing pulmonary changes at stage III had reacted positively to the test when their disease was diagnosed at other hospitals, respectively four, five and seven years earlier.

The time required for a positive reaction to develop could not be confidently assessed owing to the fact that it was not possible to keep the patients under continuous observation. As a rule, the patients were discharged from the hospital within 10 days of the application of the test antigen and re-admitted four to six weeks later for evaluation of their condition. This rather long interval was determined by the desire to obtain as definite a result as possible of the biopsy performed on the test papule. The time lapse between application of the test and biopsy averaged 39 days (range from 30 to 66 days).

Table XIX. Results of Kveim test at different stages of pulmonary sarcoidosis.

	Number of tests performed	Positive tests Number	Positive tests Per cent	Negative tests Number	Negative tests Per cent	Not performed
Stage I with erythema nodosum	23	2_	96	1	4	13
Stage I without erythema nodosum	33	29	87	4	13	8
Stage II	37	25	68	12	32	18
Stage III	3	0	0	3	(100)	5*)

*) In three of these cases sarcoidosis was previously diagnosed. A positive Kveim test had been obtained at the onset of illness.

In 1941 Kveim reported that he had made a suspension of material from a sarcoid lymph node and injected it intracutaneously into patients with sarcoidosis. A local nodule showing the histological features of sarcoidosis resulted. This reaction has been extensively studied. The first to publish important investigations were Putkonen (1943 1945) and Danbolt (1943 1948 1951). Among later significant contributions mention may be made of the papers of Chase (1961), Chase and Siltzbach (1961 1967) and Siltzbach (1961 a, 1961 b 1964). However the active principle in Kveim's test is still unknown. Test material can be produced from any human tissue affected by sarcoidosis. Since the importance of standardization of the test material is obvious, sarcoid spleen is most useful, because this organ yields material in sufficient amount.

Using standardized antigen, Kveim s test is more often positive in subacute sarcoidosis than in chronic cases (Siltzbach 1961 a). A positive reaction in diseases other than sarcoidosis is rare. In extensive control series the ratio of false positive reactions has been less than 1 per cent (Siltzbach 1967a) The majority of the patients in question have suffered from lepromatous leprosy

In 1960—1966 an international Kveim test investigation using standardized splenic antigen (Chase-Siltzbach, Type I) was carried out under the supervision of Siltzbach and participation of physicians from the U.S.A. and 37 other countries. Kveim s test was performed on a total of 3,244 subjects (Siltzbach 1967b) The reaction proved to be similar in all countries. Among the patients with positive biopsy findings (763 cases) Kveim-positivity was noted as follows: Of the patients whose illness had started with EN 63 per cent reacted positively of those who had been symptom-free when discovered by mass chest radiography 49 per cent. Kveim-positivity was noted in 62 per cent of the patients showing only BHL, in 48 per cent of those showing BHL and pulmonary mottling, and in 38 per cent of those showing mottling alone. A positive reaction was noted in 62 per cent of the patients who had a history shorter than two years and in 38 per cent of those with a longer history No correlation was observed between the tuberculin sensitivity and the Kveim reaction. 52 per cent of 145 patients who failed to react to 100—250 TU were Kveim-positive, and 54 per cent of 206 who reacted positively to 1—10 TU

In most reports from different clinics a higher degree of Kveim-positivity has been indicated than in the above-mentioned international investigation. Siltzbach (1961 b) found that 83 per cent of patients with positive biopsy results were Kveim-positive. Of those with active, subacute sarcoidosis 76 per cent reacted positively Of the patients with active chronic sarcoidosis 64 per cent and of those with inactive chronic disease 33 per cent had positive tests. Olsson, (1964), in Sweden, noted 82 per cent Kveim-positivity among patients with BHL and EN, 57 per cent among those with only BHL, 38 per cent in the group with pulmonary infiltration alone, and 11 per cent among those with pulmonary fibrosis.

In the present series, in which the same test material was used as in the above-mentioned investigations, 79 per cent of all patients showed a positive reaction. This is in agreement with the figure of 83 per cent reported by Siltzbach. The highest ratio of positive reactions was found in the group with EN just as in Olsson s Swedish series, although his figure was somewhat lower In patients without EN the frequency of Kveim-positivity was higher in the present series both at stage I and stage II. In Olsson's series a positive reaction was rarely seen in patients showing fibrotic changes, of the present patients with corresponding lesions none reacted positively The present results constitute corroborative evidence that the Kveim reaction is frequently positive in acute-subacute sarcoidosis and the positivity decreases when the disease tends to become chronic and less active. The diagnostic value of Kveim s test is reduced by the fact that the greatest diagnostic difficulties arise in cases of the last-mentioned type.

Conclusion. Kveim's test was performed in 96 cases. A positive reaction was noted in 79 per cent. The highest ratio of positivity was found in acute cases showing EN (96 per cent). In the group of patients without EN the frequency of positive reactions was higher at stage I (87 per cent) than at stage II (68 per cent). Of the three patients at stage III who were tested, all reacted negatively The ratio of positive responses was approximately the same as that reported by Siltzbach. The frequency of positivity was higher at all pulmonary stages than in a Swedish and an international study

Tuberculin sensitivity

Tuberculin sensitivity was tested with PPD-RT 23 tuberculin. Two different potencies were used. In the first test a concentration of 1 TU per 0 1 ml was used. If the result was negative, the test was repeated with 10 TU per 0.1 ml. A concentration of 100 TU per 0 1 ml was not used. The reaction was regarded as positive when the induration measured at least 10 × 10 mm.

The results of the tuberculin test at different pulmonary stages are shown in Table XX. In the group showing stage I the cases with EN have been separately analysed. As may be seen in the table, the highest tuberculin positivity was noted in the patients at stage I with EN among whom 30 per cent

Table XX. Tuberculin sensitivity in sarcoidosis at different pulmonary stages and different ages.

	PPD RT 23	–19	20–29	30–39	40–49	50–59	60–	Total	Per cent
Stage I	1 TU +	–	3	5	2	–	1	11	30
with erythema nodosum	10 TU +	–		6	5	2	–	15	42
	10 TU –	1	2		3	1	1	10	28
Stage I	1 TU +	–	–	5	4	–	–	11	27
without erythema	10 TU +	–	3			6	–	13	32
nodosum	10 TU –	–	5	7	5	–	–	17	41
Stage II	1 TU +	–	3		4	1	–	10	18
	10 TU +	–		3	4	6	–	15	27
	10 TU –	–	6	10	7	6	1	30	55
Stage III	1 TU +	–	–	–	–	–	–	0	0
	10 TU +	–	–	–	1	–	1	2	25
	10 TU –	–	–	1		2	1	6	75

reacted positively to 1 TU and a further 4 per cent to 10 TU while 28 per cent were negative even to 10 TU. Of the group at stage I without EN 27 per cent were positive to 1 TU and 3 per cent to 10 TU while 41 per cent reacted negatively to 10 TU. At stage II only 18 per cent of the patients were positive to 1 TU and 55 per cent did not react to 10 TU. Of the eight patients at stage III six (75 per cent) failed to react to 10 TU.

On comparison with the distribution of tuberculin positivity in a normal series with the same age distribution and from the same geographical area (Fig. 14), an obvious difference in the pattern was observed in all age groups. In the normal series, which consisted of 1,58? patients (collected by Hellström and Repo), the lowest frequency of tuberculin positivity to 1 TU was found in the 20–29 age group. This figure is 55 per cent while 29 per cent of the sarcoidosis patients of the same age group were positive to 1 TU irrespective of pulmonary stage. In the 40–49 age group a positive reaction to 1 TU was noted in 79 per cent of the normal series against only 26 per cent of the patients with sarcoidosis. No reaction to 10 TU was seen in about 40 per cent of the sarcoidosis patients irrespective of age, while in the normal series less than 10 per cent were negative to 10 TU.

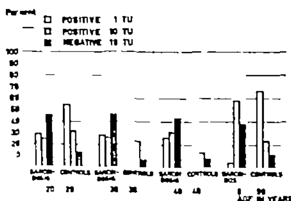


Fig. 14. Percentual distribution of tuberculin sensitivity in different age groups in sarcoidosis and in control series.

On comparison of the sarcoidosis and normal series the most significant observation is that in the latter the tuberculin positivity was high irrespective of age, while in the sarcoidosis series a depression of the reaction and a clear increase in tuberculin negativity was noted. On comparison of the groups, significant differences emerged, but in the individual case the tuberculin reaction lacks diagnostic significance.

It has been known since the time of Boeck (1905) that the tuberculin reaction may be depressed in sarcoidosis. Many relevant investigations have been published. Reisner (1944) found that 60 per cent of 35 New York patients were negative to 100 TU *). *Ricker and Clark (1949) reported tuberculin negativity* in 97 per cent of 88 patients tested. Cowdell (1954) in England found that 65 per cent of 49 patients were negative to 100 TU. Of 156 patients studied by Israel and Sones (1958) 6 per cent were positive to 1 TU, 22 per cent were positive to 250 TU and 72 per cent failed to react to 250 TU. Among 60 sarcoidosis patients tested by Scadding (1967), 4 per cent reacted positively to 1 TU, 14 per cent were positive to 10 TU, 1 per cent were positive to 100 TU and 61 per cent failed to react to 100 TU. Wurm (1963) tested 800 patients and noted positivity

*) The tuberculin sensitivity which in earlier studies was indicated in different dilutions of Old Tuberculin, has been calculated as TU units of PPD for the sake of comparison. 1 TU (tuberculin unit) = 0.00002 mg purified protein derivative (PPD) = 0.1 ml Old Tuberculin in dilution 1:10,000 = 0.01 mg Old Tuberculin.

to 0.01–0 1 TU in 2 per cent and positivity to 1 TU in 7.5 per cent, while 18.6 per cent reacted positively to 10 TU and 27 4 per cent to 100 TU Tuberculin negativity was noted in 44.5 per cent.

When testing 212 Swedish sarcoidosis patients with BHL, Löfgren and Lundbäck (1952 b) found that 18 per cent reacted positively to 1–5 TU and 35 per cent to 10–100 TU while 47 per cent showed no reaction to 100 TU Rudberg-Roos (1962) tested 204 patients, 60 per cent of whom were negative to 100 TU while 77 per cent failed to react to 10 TU

In connection with the International Kveim investigation 1960–1966, certain clinical data were also reported (Siltzbach 1967b). In regard to tuberculin sensitivity wide variations were observed between the different countries. The highest rate of tuberculin-positive cases was noted in the Finnish series, in which 60 per cent reacted to 1–10 TU and a total of 68 per cent of the patients were tuberculin-positive. From Denmark a tuberculin-positivity of 63 per cent was reported, and 56 per cent showed a positive reaction to 1–10 TU In the Hungarian and Swedish series 54 per cent and 53 per cent, respectively reacted positively to tuberculin of various potencies. By contrast, in Czechoslovakia, Eire, Poland, France and Uruguay 75 per cent or more of the patients were entirely tuberculin-negative. Many of the groups investigated were small, however

The present results confirm the tendency observed in the international investigation. There was an obviously higher degree of tuberculin positivity than in investigations from other countries. In the early stage of sarcoidosis (BHL with and without EN) the ratio of tuberculin-positivity was much higher in the present series than in the Swedish series described by Löfgren and Lundbäck (1952 b), and Rudberg-Roos (1962) also noted a higher degree of tuberculin-negativity in her series, which otherwise closely resembled the present one.

The high degree of tuberculin-positivity observed among Finnish sarcoidosis patients is probably accounted for by the facts that there are still persons with contagious tuberculosis in the community who contribute to the maintenance of a natural tuberculin-positivity and that BCG vaccination is carried through to about 100 per cent.

Conclusion As compared to a normal series, the sarcoidosis patients exhibited reduced tuberculin sensitivity The tuberculin test lacks diagnostic significance in the individual case. The slightest reduction in tuberculin sensitivity was noted in acute cases with EN When the disease tends to become chronic, tuberculin negativity seems to increase. The degree of tuberculin positivity was higher in the present Finnish series than in the sarcoidosis series reported from other countries.

Biopsy aspects

Tissue biopsies were performed in 124 cases, and a total of 278 specimens were examined. The most frequent objects of biopsy were bronchial mucosa and lymph nodes. Specimens from other organs were taken mainly when gross changes or laboratory results constituted evidence of some particular organ manifestation. In addition, a specimen of the gastrocnemius muscle was taken in some cases showing EN and renal biopsy was performed in some acute cases. Bone marrow puncture was routinely performed in some cases.

The biopsy results are shown in Table XXI. Changes consistent with sarcoidosis were observed in 43 per cent of all specimens.

Lymph node biopsy was performed in 65 cases. The specimen was taken in connection with mediastinoscopy in five. Changes typical of sarcoidosis were found in all five cases. In 20 cases a palpable node was investigated. Unspecific inflammation was noted in one case only while the remaining 19 offered evidence of sarcoidosis. In these, chest radiographs showed changes (Table XXII) of stage I in six cases, stage II in 12 cases and stage III in one case.

A biopsy specimen of the prescalene fat pad was taken in 40 cases. In five of these only fatty tissue was obtained. At stage I 15 specimens of 24 (62 per cent) were positive, at stage II, seven of 15 (47 per cent) were positive. The only biopsy performed at stage III gave a negative result (Table XXII)

The biopsies of the bronchial mucosa are discussed on p. 34 the renal biopsies on p. 40

In 14 cases showing EN a specimen was taken of the gastrocnemius muscle. The result was positive in four Sternal puncture was likewise performed in 14 cases, but no epithelioid cells were seen. The remainder of the biopsies were performed in occasional cases exhibiting signs of involvement of some special organ. Thoracotomy and lung biopsy was carried out in one case only

Enlarged peripheral lymph nodes are a relatively frequent finding in sarcoidosis. Ratios varying from 56 to 100 per cent have been reported in North American series (Mayock et al. 1963). Mayock et al. themselves noted peripheral lymphadenopathy in 88 per cent of 145 cases. In European series lower frequencies have been noted. James (1956) observed palpable peripheral nodes in 37 per cent of 150 cases, Smellie and Hoyle (1960) in 30 per cent of 125 cases and Scadding (1967) in 31 per cent of 275 cases. Rudberg-Roos (1962) found enlarged peripheral lymph nodes in 28 per cent of 204 patients. Löfgren and Snellman (1964) stated that on careful investigation it is probably possible to detect palpable nodes

Table XXI. Results of biopsies performed in 1 4 cases of sarcoidosis with intrathoracic changes.

	Number of biopsies performed	Number of positive biopsies	Number of negative biopsies	Positive biopsies. Per cent
Lymph node biopsies				
Mediastinoscopy	5	5	0	100
Palpable node	20	19	1	95
Daniels method	40	22	18	55
Bronchial mucosa	148	48	100	3
Nasal mucosa	2	1	1	
Tonsil	3	1	2	
Gastrocnemius muscle	14	4	10	8
Bone marrow	14	0	14	0
Cicatricial tissue	5	4	1	
Skin	7	4	3	
Conjunctiva	1	1	0	
Kidney	16	7	9	44
Liver	2		0	
Lung	1	1	0	
Total	278	119	159	43

Table XXII Results of lymph node biopsy (biopsy of palpable nodes and biopsy by Daniels method) in sarcoidosis at different pulmonary stages.

	Stage I	Stage II	Stage III	Total
Palpable node				
Positive	6	1	1	19
Negative	—	1	—	1
Daniels method				
Positive	15	7	—	22
Negative	9	8	1	18

in 70 per cent of all patients suspected of sarcoidosis, but they gave no figures of their own.

Palpable lymph nodes may easily be removed for histological investigation. This has proved to be a statisfactory method in sarcoidosis. Löfgren and Snellman (1964) obtained positive results in 89 per cent of their cases (173 positive specimens of 194). Israel and Sones (1964) reported a similar result: 17 positive specimens out of 200 (86 per cent). Scadding (1967) obtained positive biopsy results in 9 per cent of his cases. The present series is scanty as compared to those cited above but the ratio of positive biopsies performed on peripheral, palpable lymph nodes is of the same order

Daniels (1949) introduced the method of surgically removing the prescalene fat pad containing small lymph nodes as an aid in the patho-anatomical diagnosis of pulmonary diseases. This method has been tested in sarcoidosis by many authors, with variable results. Carstensen et al. (1956) obtained a positive specimen in 148 cases of 37 (6 per cent). Lillington and Jamplis (1963) compiled the results of 14 reports and found that biopsy had been positive in 83 per cent (138 patients). Israel and Sones (1964) obtained a positive specimen in 40 cases of 54 (74 per cent) while Löfgren and Snellman (1964) noted positive results in 15 cases of 47 (32 per cent). Rudberg-Roos (196) ratio of positive specimens was 68 per cent in a series of 204 Gebel (1965) obtained 58 positive specimens among 75 taken (77.5 per cent), and the distribution of the results by pulmonary stage was as follows: 3 positive of 28 (82 per cent) at stage I, 5 positive of 35 (71 per cent) at stage II, and 10 positive of 12 (83 per cent) at stage III. Scadding (1967) noted positive results in 20 out of 4 biopsies performed (83 per cent).

In the present series 22 biopsies of 40 were positive (55 per cent). This is a poorer result than any of those cited above, except that of Löfgren and Snellman (1964) At stage I better results (62 per cent) were obtained than at stage II (47 per cent). The tendency is the same as in Gebel's (1965) series, but the number of specimens examined is smaller at both stages. In explanation of the poorer results obtained in the present series as compared to many others it can hardly be alleged that in Finland sarcoidosis is not disseminated to the prescalenic nodes to the same degree. The discrepancy seems rather to be accounted for by the small number of biopsies and by the fact that Daniel's operation is admittedly technically difficult.

Mediastinoscopy which was introduced by Carlens (1959), has proved to be very useful in the diagnosis of sarcoidosis. The ratios of positive specimens reported have exceeded 90 per cent (Carlens 1964 Israel and Sones 1964 Löfgren and Snellman 1964 Pätiälä 1964). In the present series only five mediastinoscopies were performed, the finding was consistent with sarcoidosis in all.

Myers et al. (1952) drew attention to the fact that the skeletal muscles can be infiltrated by epithelioid cell granulomas in sarcoidosis even though the patient shows no clinical signs of muscular disease. Wallace et al. (1958) found granulomas in the musculature in 23 patients of 42 (55 per cent). Of six patients with EN five exhibited specific changes. Muratore (1964) observed changes in eight patients of nine. Mayock et al. (1963) detected massive sarcoid infiltration in the musculature in three patients, but they found no specific changes on random biopsy in symptomless cases. The number of biopsies was not indicated, however Israel and Sones (1964) reported nine positive biopsies among 13 (69 per cent).

Since it appears that no extensive systematic studies of the muscular changes in sarcoidosis have been performed, no reliable frequency figures are available. It is obvious, however that the skeletal muscles, like many other organs, may be affected even in asymptomatic cases. In the present series the result of biopsy was positive in four cases of 14 (28 per cent).

On comparison of different biopsy methods it is found that the highest ratio of positive results, irrespective of pulmonary stage was obtained by biopsy of palpable lymph nodes and by investigation of lymph nodes obtained in connection with mediastinoscopy Biopsy of the prescalene fat pad gave positive results in somewhat over half the cases. The ratio of positive results was slightly higher at stage I than at stage II The biopsies of bronchial mucosa (p. 34) were also positive in half the cases, but the results were considerably better at stage II than at stage I. If gross lesions are present in other organs (skin, subcutaneous nodules, conjunctiva) these will of course first be the object of biopsy

The erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) was determined in the morning the day after admission and read after one hour The results were classified by pulmonary stage and occurrence of EN It was not possible to correlate the ESR to the duration of illness, since in many cases this could not be confidently established (cf p. 30)

As may be seen in Table XXIII, an ESR ≥ 41 mm/h was noted in 25 patients (18 per cent) Of these, 19 (76 per cent) showed EN An ESR under 15 mm/h was observed in 54 patients (39 per cent), only three of whom had EN Discounting the small number of patients at stage III about 40 per cent — irrespective of pulmonary stage — had an ESR between 16 and 40 mm/h, which may be regarded as a moderate elevation.

In regard to stage I it is noteworthy that elevation of the ESR was dependent on the occurrence of EN In the group showing EN only 8 per cent had an ESR under 15 mm/h, while among the patients without EN only four patients (10 per cent) had an ESR over 40 mm/h. At stage II a normal or moderately elevated ESR was noted in over 90 per cent of the cases. Only four patients had a high ESR, and two of these showed EN

In earlier series of sarcoidosis, North American ones in particular an elevated ESR has frequently been observed. Among 52 patients Ricker and Clark (1949) noted a normal ESR in 20 values over 11 mm/h in 32 and values over 30 mm/h in 14 In a survey of earlier series from the U.S.A. Mayock et al. (1963) found elevation of the ESR in an average of 61 per cent of the cases.

In a series of 204 patients Rudberg-Roos (1962) noted an ESR under 20 mm/h in well over half the cases. Elevation over 50 mm/h was observed in 20 patients, 17 of whom were acute cases. Two of these patients had lupus pernio and one had diabetes insipidus.

Löfgren (1953 a) analysed the erythrocyte sedimentation rates determined within three weeks from the onset of illness in »primary sarcoidosis» No case of EN (113 patients) had an ESR under 15 mm/h.

Table XXIII. Erythrocyte sedimentation rate on admission to hospital in sarcoidosis at different pulmonary stages.

	1—15 mm/h		16—40 mm/h		41 — mm/h		Total
	No. of pat	Per cent	No. f pat	Per cent	No. of pat	Per cent	
Stage I with erythema nodosum	3	8	16	45	17	47	36
Stage I without erythema nodosum	21	51	16	39	4	10	41
Stage II	27	49	22	44	4)	7	55
Stage III	3		5		0		8
Total	54	39	61	43	25	18	140

) Two of these patients had erythema nodosum.

Values between 15 and 24 were noted in seven cases, values between 25 and 49 in 15 cases, values between 50 and 99 in 36 cases and values over 100 mm/h in 24 cases. An ESR over 50 mm/h was measured in only three patients among those who had been symptom-free when their disease was discovered by mass radiography and those who had presented with symptoms other than EN (a total of 75). An ESR under 15 mm/h was found in 34 cases.

In the present series a high ESR was observed mainly in the patients showing EN as in Löfgren's series and in acute cases in Rudberg-Roos series. In patients without EN an ESR between 1 and 15 mm/h was measured in 50 per cent and an ESR of 16–40 mm/h in 44 per cent which is in agreement with the results in the two above-mentioned Swedish series. In the U.S.A. EN is rare in sarcoidosis, but an elevated ESR has still been noted in over half the cases. This is probably due to the fact that the North American series consist predominantly of negroes, who show greater changes in the electrophoretic pattern of the serum proteins than whites (hypoalbuminaemia, hypergammaglobulinaemia, cf. p. 50).

Conclusion. Of the present patients 39 per cent had an ESR of 1 15 mm/h and 18 per cent had values over 40 mm/h. Of the latter group of 25 patients, 19 showed EN A high ESR was mainly seen in connection with EN which is in agreement with the results in earlier Scandinavian reports. In sarcoidosis without EN an ESR ≤ 15 mm/h was measured in half the cases, while only 6 per cent had an ESR over 40 mm/h. The ESR lacks diagnostic significance in sarcoidosis.

Serum protein and protein electrophoresis

The serum total proteins were determined by the biuret method. The protein fractions were separated by paper electrophoresis using standard methods (Veronal buffer pH 8.6) and a standard LKB electrophoretic set.

The sarcoidosis patients were classified according to pulmonary stage. The patients at stage I showing EN were classified as a separate group. A control group comprising 40 healthy subjects consisted of volunteers from the hospital personnel and subjects admitted to the Fourth Department of Medicine for investigation of their suitability as kidney donors. In the case of hospitalized patients and controls fasting samples were collected in the morning before rising. The values given for the sarcoidosis patients are those obtained at the first investigation after admission.

The results are compiled in Table XXIV This shows the mean values in each group ± the standard error of the mean value. In addition, it shows the standard deviation and the significance of the difference on comparison with the control group. Significance was tested by the t test.

Total proteins

The individual values for total protein appear in Fig 15 The groups at stage I with EN and at stage I without EN consist of 33 patients each. The group at stage II comprises 49 the group at stage III nine patients. In the last-mentioned group eight values represent the condition on admission to hospital,

Table XXIV Serum proteins and electrophoretic fractions (g/100 ml) in sarcoidosis at different pulmonary stages. Mean values ± standard error of mean and standard deviation (below) are indicated. The degree of significant differences is indicated by (= highly significant $P < 0.001$ = significant $P < 0.01$ = probably significant, $P < 0.05$).

	Total protein	Albumin	Alpha	Alpha$_2$ Globulins	Beta	Gamma
Controls	7.1 ± 0.06 0.38	4.10 ± 0.07 0.44	0.36 ± 0.01 0.06	0.53 ± 0.01 0.09	0.80 ± 0.02 0.13	1.24 ± 0.03 0.16
Stage I with erythema nodosum	7.3 ± 0.08 0.45	3.4 ± 0.09 0.54	0.39 ± 0.02 0.13	0.86 ± 0.04 0.22	1.05 ± 0.04 0.24	1.61 ± 0.05 0.27
Stage I without erythema nodosum	7.2 ± 0.1 0.68	3.65 ± 0.09 0.50	0.35 ± 0.02 0.1	0.75 ± 0.03 0.18	0.98 ± 0.04 0.20	1.50 ± 0.06 0.33
Stage II	7.4 ± 0.08 0.57	3.70 ± 0.07 0.50	0.34 ± 0.02 0.11	0.76 ± 0.03 0.18	0.98 ± 0.03 0.18	1.61 ± 0.05 0.34
Stage III	7.1 ± 0.20 0.59	3.46 ± 0.18 0.53	0.37 ± 0.03 0.10	0.77 ± 0.07 0.21	0.88 ± 0.07 0.22	1.59 ± 0.09 0.27

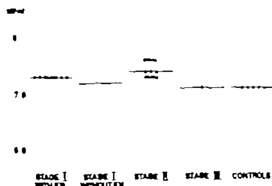


Fig 15 Total serum protein in sarcoidosis t different pulmonary stages and in a control series. Horizontal lines indicate mean values.

while one patient did not develop stage III until later

As may be seen in the figure, total protein values over 8 g/100 ml were observed in one patient at stage I with EN in four patients at stage I without EN and in five patients at stage II. Values under 6 g/100 ml were noted in two cases. The mean values lie between 7 1 and 7 4 g/100 ml No statistically significant differences were observed.

Albumin

The values for the albumin fraction obtained by paper electrophoresis are shown in Fig. 16. In all sarcoidosis groups the level is decreased to a statistically highly significant extent. The differences between the various sarcoidosis groups are not significant.

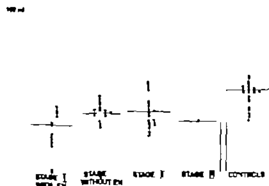


Fig 16. Serum albumin in sarcoidosis t different pulmonary stages and in control series. Horizontal lines indicate mean values.

Alpha$_1$ globulin

The absolute values for the alpha$_1$ globulin fraction in the individual cases appear in Fig. 17 The mean alues in all groups lie within the normal range. The differences between the sarcoidosis groups and the normal group, and between the various sarcoidosis groups, are not statistically significant.

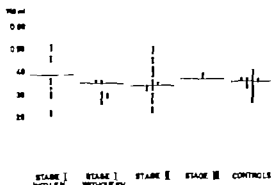


Fig 17 Serum alpha globulin in sarcoidosis t different pulmonary tages and in a co trol series. Horizontal lines indicate mean values.

Alpha$_2$ globulin

The absolute values for alpha$_2$ globulin in the individual cases are shown in Fig 18. The highest mean value was noted in the group with pulmonary changes at stage I and EN The difference between this and the normal group is statistically highly significant. Highly significant differences were also noted between stage I without EN and the controls and between stage II and the normal group. The difference between stage III and the normal group is significant. The difference between stage I with EN and stage I without EN is statistically insignificant.

Immune electrophoresis was performed in six cases at stage I showing EN and obviously increased alpha$_2$ globulin. A definite, though unspecific increase in haptoglobin was observed.

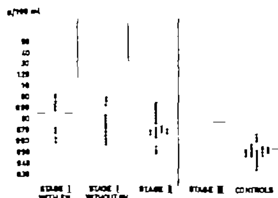


Fig 18 Serum alpha$_2$ globulin in sarcoidosis at different pulmonary stages and in a control series. Horizontal lines indicate mean values.

Beta globulin

The absolute values for beta globulin in the individual cases appear in Fig. 19 The highest mean value was noted in the group at stage I with EN Highly significant differences were observed between the normal group and the groups at stage I with and without EN and the group at stage II No significant differences were noted between the different sarcoidosis groups.

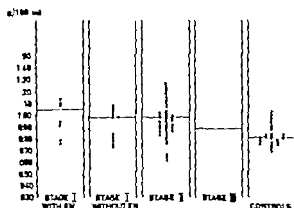
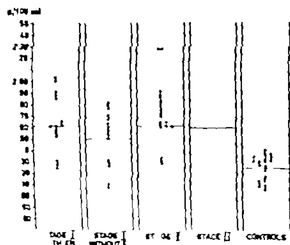


Fig 19 Serum beta globulin in sarcoidosis t different pulmonary stages nd in a control series. Horizontal lines indicate mean lues.

Gamma globulin

The absolute values for gamma globulin appear in Fig. 20 As compared to the normal group, elevated mean values were noted in all sarcoidosis groups. The differences are statistically highly significant. On the other hand the differences between the various sarcoidosis groups are insignificant.



F g 20 Serum gamma globuli in sarco dosis at different p lmonary stages and in co trol series. Horizon l l es indicat mean alues

Salvesen (1935) described three patients with sarcoidosis who had high serum protein values (9 0–9 7 mg/100 ml) and high globulin values (5.05–6.10 mg/100 ml). His results were corroborated by Harrell and Fisher (1939) and Ricker and Clark (1949), among others, who also noted elevated total protein and globulin values, although not so high as those reported by Salvesen.

Seibert and Nelson (1943) and Seibert et al. (1947), who carried out electrophoretic investigations in sarcoidosis and other chronic diseases, observed in sarcoidosis an increase in total proteins, a decrease in albumin and an increase in gamma globulin. *Since they did not find exactly the same pattern in* any other disease, they concluded that the method had a certain diagnostic significance. Sunderman and Sunderman (1957) also reported high total protein, a decrease in albumin and a step-like pattern of increasing concentration from $alpha_1$ to gamma globulin McCuiston and Hudgins (1960) observed the same globulin pattern. Johnson and Wakefield (1962) who compared the electrophoretic pattern of the serum proteins among negro and white sar coidosis patients in the U.S.A., found that the whites had the same total protein level as a normal series, while the negroes had clearly elevated total protein values. Norberg (1964) in Sweden studied the serum proteins in different stages of sarcoidosis (BHL, disseminated pulmonary infiltration, pulmonary fibrosis) by a conventional paper electrophoretic technique. She found an increase in total proteins in progressive disease, but the samples were collected from ambulant patients, and when these values were compared to the values obtained on samples collected before the patients had got up, the former were found to be higher to a statistically significant extent. The albumin level was decreased and the $alpha_2$ globulin level increased in all patient groups. An increase in beta globulin was noted in many cases in each group. Gamma globulin showed an increase only in the groups with progressive disease. Later Norberg (1967) investigated the serum proteins in patients with sarcoidosis and EN using zone elec trophoresis in polyvinyl chloride. The total protein level was the same in sarcoidosis as in a control group. The albumin level showed a statistically highly significant decrease, while the $alpha_1$ and $alpha_2$ globulins were increased to a statistically highly significant extent and the beta globulin showed a significant increase as compared to the control series. No significant difference was observed in regard to gamma globulin.

In the present series the mean value for *total protein* was within the normal range in all groups examined, and no statistically significant difference was observed on comparison with a normal control

group. In the group with EN the result was the same as that reported by Norberg (1967). By contrast, Norberg (1964) noted elevated total protein values in progressive cases without EN but in 10 cases of sarcoidosis she showed, on the other hand, that the total protein level was 14.5 per cent higher when the samples were collected after the patients had got up If her values are correspondingly reduced the mean values fall within the normal range. Normal values were also reported by Johnson and Wakefield (1962) in a study of whites in the U.S.A. It thus appears that elevated total protein values have mainly been observed in sarcoidosis in negroes. Occasional high values have been noted at all stages of sarcoidosis, but the groups as a whole do not differ from normal control groups.

The *albumin* level showed a statistically highly significant decrease in all groups, as compared to the normal control series. The same observation has been made by all investigators cited above.

Alpha₁ globulin was within the normal range in all groups and did not differ from the pattern observed in the normal series. Similar observations were reported by Norberg (1964) although in a later study (1967) she noted elevated values in patients with sarcoidosis and concomitant EN This was probably due to the fact that she used a more sensitive technique than previously permitting better separation of the fractions. By conventional paper electrophoresis increased alpha$_1$ globulin values have not been noted in sarcoidosis.

Alpha$_2$ globulin was increased in all groups. Patients with concomitant EN showed the greatest increase. This is in agreement with the results reported by Norberg (1964 1967). The patients with renal sarcoidosis did not differ from the remainder in regard to the increase in alpha$_2$ globulin.

The *beta globulin* level was also elevated in all groups except in that showing stage III. The greatest increase was observed in the group with EN This is in agreement with Norberg's results (1967), but the difference was highly significant in the present series and significant in hers. In patients not showing EN Norberg (1964) noted significantly elevated values in cases with BHL in progressive phase and in cases with disseminated pulmonary infiltration and fibrosis in stationary phase, but not in the group with BHL in stationary phase or in patients with disseminated pulmonary infiltration or fibrosis in progressive phase. It is noteworthy however that in Norberg's series no significant differences were observed between the various groups with disseminated pulmonary infiltration nor between the various groups with fibrotic changes. A probably significant difference was noted between the two groups with BHL.

Increased *gamma globulin* is a finding frequently reported in earlier paper electrophoretic investigations of patients with sarcoidosis (Seibert et al. 1947 Sunderman and Sunderman 1957 Mc Cuiston and Hudgins 1960) By contrast, Norberg (1964) noted an elevated gamma globulin level only in cases showing fibrotic changes or disseminated pulmonary infiltration in progressive phase. She did not observe any increase in gamma globulin in the presence of concomitant EN The present results differ from those of Norberg in that elevated values were observed in all groups, including the group with EN

As compared to the investigations (Sunderman and Sunderman 1957 McCuiston and Hudgins 1960) in which a steplike pattern of increasing concentration from alpha$_1$ to gamma globulin was observed, it should be pointed out that no such pattern was seen in the present study in which the increase in alpha$_2$ globulin was most marked. Relatively speaking, the increase in beta globulin was the next largest and larger than the increase in gamma globulin. The level of alpha$_1$ globulin was within the normal range. This pattern is more like the results reported by Norberg.

Conclusion The serum total protein and the various protein fractions were determined in different groups of sarcoidosis patients (BHL with EN BHL without EN stage II and stage III). The mean values for total protein and alpha$_1$ globulin were within the normal range in all groups. Albumin was decreased in all groups. The alpha$_2$, beta and gamma globulin levels were elevated in all groups with the exception of beta globulin at stage III. Alpha$_2$ globulin showed the most marked increase. A steplike increase of globulin from alpha$_1$ to gamma, as has been reported in earlier studies by other authors, was not observed in the present series. The results are mainly comparable to those reported by Norberg in her detailed studies on the serum proteins in sarcoidosis. Taking into account certain differences in technique and classification of the cases, it may be stated that the results are in agreement, except that elevated gamma globulin values were more frequently observed in the present series.

The latex fixation test

The latex fixation test was performed in 90 cases of sarcoidosis. The results are shown in Table XXV At stage I three positive reactions were observed among 45 female patients. None of the eight men in this group had a positive test. One of the women with a positive test showed EN In the group at stage II 32 tests were performed. Six positive reactions were noted among 19 female patients, none among 13 male patients. At stage III one of two women and

Table XXV Latex fixation test in sarcoidosis at different pulmonary stages in the two sexes.

	Stage I No. of tests performed	No. of positive tests	Stage II No. of tests performed	No. of positive tests	Stage III No. of tests performed	No. of positive tests	Total No. of tests performed	No. of positive tests
Women	45	3	19	6	2	1	66	10 (15 per cent)
Men	8	0	13	0	3	1	24	1 (4 per cent)
Total	53	3	32	6	5	2	90	11 (12 per cent)

one of three men had positive test results. A total of 10 positive reactions among 66 women (15 per cent) and one among 24 men (4 per cent) were thus observed.

Kunkel et al. (1958) reported positive latex fixation tests in six of 61 patients investigated. All six were women with chronic sarcoidosis. In the series described by Müller et al. (1961) the test was positive in 18 per cent of 244 cases. Israel et al. (1964) noted positive results in three of 16 men (19 per cent) and 21 of 35 women (60 per cent). Positive results were observed both in patients with BHL alone and in chronic cases.

The results in the present series are in agreement with those of Israel et al. in that positive tests were obtained at any stage of sarcoidosis. This is also consistent with the finding that the gamma globulin level may be increased in all forms of the disease. The fact that the frequency of positive latex fixation tests was higher in the North American series must be considered against the background of the composition of the two series, the latter consisting of 49 negroes and only two whites. The sex distribution is similar. The test is more frequently positive in women. The cause of this is obscure, but it seems possible that a constitutional factor is involved, which is also reflected in the higher frequency of sarcoidosis in women.

Serum calcium

Serum calcium was determined by EDTA titration using Cal-Red as indicator (Patton and Reeder 1956). In the first investigations performed on patients at the Mjölbolsta Hospital, $KMnO_4$ titration by the method of Kramer and Tisdall (1921) was used.

A total of 133 sarcoidosis patients were investigated. The distribution by pulmonary stage was as follows: stage I 73 patients, stage II 52 patients, stage III eight patients. In addition, 45 healthy controls were investigated.

In the sarcoidosis series a total of 356 determinations were performed. Fig. 21 shows the individual mean values for all patients and the mean values for the groups. At stage I a mean value exceeding 11.0 mg/100 ml was noted in six cases (8 per cent). In a further six cases one elevated value (over 11.0 mg/100 ml) was obtained, but in these cases the mean value of several determinations was under 11.0 mg/100 ml. Four patients had mean values under 9.0 mg/100 ml.

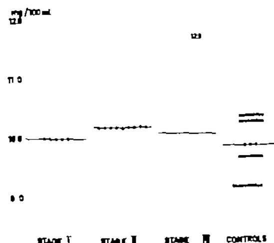


Fig. 21. Serum calcium in sarcoidosis at different pulmonary stages and in a control series. Horizontal lines indicate mean values.

At stage II elevated mean values were observed in six patients (11 per cent). A further four patients had occasional values over 11 mg/100 ml. Three patients had mean values under 9 mg/100 ml.

The highest mean value in the whole series, 12.9 mg/100 ml, was obtained in a patient at stage III. In this group, which consisted of only eight patients, a mean value under 9 mg/100 ml was noted in one case.

In the control group of 45 healthy subjects the mean value was 9.9 mg/100 ml. In one case the mean value exceeded 11 mg/100 ml, while in two cases a mean value under 9 mg/100 ml was noted.

Table XXVI shows the mean values ± the standard error of mean in the various sarcoidosis groups and in the normal control group. The standard deviation is also indicated. The difference between the serum calcium values in the control group and in sarcoidosis at stage II is statistically almost significant, while no significant differences were noted between the other groups of sarcoidosis and the controls. *The mean values for all groups, however* lie within the normal range.

Table XXVI. Serum calcium, serum phosphorus and urinary calcium at different stages of pulmonary sarcoidosis. Mean values ± standard error of mean and standard deviation (below). The degree of *significant differences is indicated* by (see Table XXIV).

	Serum calcium mg/100 ml	Serum phosphorus mg/100 ml	Urinary calcium mg/24 h
Controls	9.9 ± 0.07 0.45	4.4 ± 0.08 0.52	125 ± 8 54
Stage I	10.0 ± 0.08 0.69	3.3 ± 0.07 0.53	165 ± 14 104
Stage II	10.2 ± 0.10 0.69	3.5 ± 0.10 0.58	175 ± 17 114
Stage III	10.1 ± 0.45 1.28	3.3 ± 0.16 0.41	

Urinary calcium

Before determination of the urinary calcium excretion the patients were given a low calcium diet at least two days. The same method of determination was used as for serum calcium. An excretion exceeding 250 mg/24 h was regarded as elevated. Determinations were performed on 58 patients at stage I, 44 patients at stage II and five patients at stage III. In addition, 45 normal cases were studied. A total of 228 determinations were performed in the sarcoidosis series. For each patient the mean value of all determinations was calculated. The results are shown in Table XXVII.

All values in the control series were under 250 mg/24 h. Of the patients at stage I nine (16 per cent) had mean values exceeding 250 mg/24 h (six under 300 mg, three over 350 mg). Another two patients had respectively one and two values exceeding 250 mg/24 h, but the mean values were under 250 mg.

Eight of the patients at stage II (18 per cent) had a urinary calcium excretion exceeding 250 mg/24 h. In another five cases higher readings were obtained at least once but the mean values did not reach this level.

Only five patients with pulmonary changes corresponding to stage III were investigated. One of these had elevated urinary calcium values throughout. Two of the remainder had an elevated value at one determination, but the mean value was under 250 mg/24 h.

The mean values for the various patient groups appear in Table XXVI. In addition, the standard error of the mean value and the standard deviation are given. As compared to the normal control series, the excretion was increased to a statistically almost significant extent at stage I and to a significant extent at stage II. The mean values, however lie within the normal range.

Harrell and Fisher (1939) were the first to describe hypercalcaemia in sarcoidosis. In North American series varying frequencies of hypercalcaemia have been reported. Cummings et al. (1959) noted values over 11 mg/100 ml in 35 per cent of 113 patients and *Mayock et al. (1963) noted such values in 19* per cent of 91 patients. Intermediate figures have been indicated by other authors.

In England Scaddmg (1967) found that six patients among 62 had serum calcium values exceeding 11 mg/100 ml and six had a level of 11 mg/100 ml, while in six cases values of 9 mg/100 ml or less were noted. James (1956) found among 150 patients only one with persisting hypercalcaemia. In a series of sarcoidosis patients with EN James (1961b) later observed hypercalcaemia exceeding 11 mg/100 ml in eight patients of 72 investigated, but he did not find

Table XXVII. Daily urinary excretion of calcium (mean values of several determinations) in sarcoidosis at different pulmonary stages and in controh. The number of patients in each group is indicated.

	Urinary calcium g/24 h. −50	51−100	101−150	151−200	201−250	251−300	301−350	351−	Total
Stage I	2	14	16	11	6	6	0	3	58
Stage II	4	11	6	8	7	2	3	3	44
Stage III	1	1	0	0	2	0	1	0	5
Stages I−III	7	26	22	19	15	8	4	6	107
Controls	4	16	11	11	3	0	0	0	45

hypercalciuria over 300 mg/24 h in any case of 11 investigated.

Of Scandinavian authors Rudberg-Roos (196_) in Sweden, noted serum calcium values over 11 mg/100 ml in 43 patients of 185. Hypercalcaemia was observed in 10 per cent of acute cases and in 20 per cent among the remainder. In Finland, Putkonen et al. (1965b) observed only two cases of hypercalcaemia at their first examination of 60 patients, and both showed normal values at check-up two months later. On the other hand, they noted hypercalciuria over 300 mg/24 h in six patients of 39 investigated (15 per cent). In the same paper Putkonen et al. reviewed the earlier literature on this subject.

In the present series hypercalcaemia (a mean value of several determinations exceeding 11 mg/100 ml) was observed in 9 per cent of the patients. Elevated values were noted in both acute and chronic cases. The frequency is in agreement with the results reported by Scadding in England (10 per cent) and by Rudberg-Roos in Sweden. By contrast, hypercalcaemia was more frequent than in the English series described by James and the Finnish series described by Putkonen et al. As compared to the U.S.A., hypercalcaemia seems to be less frequent in England and Scandinavia.

The varying results may in part be accounted for by the fact that the determination is technically difficult. Results obtained by the same technique vary from one laboratory to another. Furthermore it is not obvious in all reports whether the values given are the result of one or more determinations. It is a well-known fact that an occasional elevated value is often obtained although the result at check up may be normal. It is noteworthy however that the present results differ from those reported by Putkonen et al. in their Finnish series.

In the present series hypercalciuria was observed in 18 patients of 107 investigated (17 per cent). Hypercalciuria occurred at all stages of sarcoidosis. The ratio is in agreement with that (15 per cent) reported by Putkonen et al. (1965 b) in Finnish patients. No other extensive series are available for comparison.

Conclusion. Hypercalcaemia and hypercalciuria were seen at all stages of sarcoidosis. Hypercalcaemia was noted in 9 per cent and hypercalciuria in 17 per cent of the patients. The ratio of hypercalciuria is the same as in an earlier report from Finland. Hypercalcaemia has been observed both more and less frequently than in the present series.

Serum phosphorus

Inorganic serum phosphate was determined by the method of Fisk and Subbarow (19_5).

Ninety-four sarcoidosis patients were investigated. Patients with impaired renal function were excluded. A total of _14 determinations were performed. The mean value of several determinations was calculated for each patient. In addition, serum phosphorus was determined in 45 normal controls.

Fifty-three of the patients studied had pulmonary changes at stage I. The results are shown in Fig. 22. A value under _8 mg/100 ml was noted in six cases. No pathologically high values were obtained. Of the patients at stage II (34 cases), four had mean values under _8 mg/100 ml. Seven patients at stage III were studied. Two of these had mean values under 2.8 mg/100 ml. There was no correlation between the low serum phosphorus values and serum calcium values exceeding 11.0 mg/100ml.

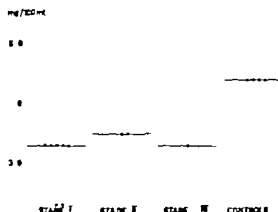


Fig. 22. Serum phosphorus in sarcoidosis at different pulmonary stages and in control series. Horizontal lines indicate mean values.

Table XXVI shows the mean values ± the standard error of the mean and the standard deviation. As compared to the control group, a statistically highly significant decrease of the serum phosphorus values was seen in all sarcoidosis groups. The majority of the absolute values, however, lie within the normal range.

Serum phosphorus has been studied much less than serum calcium. Those who have determined serum phosphorus in sarcoidosis have noted normal values (e.g. Harrell and Fisher 1939). However, Longcope and Freiman (195_) reported varying and occasionally low values. In 22 patients from Baltimore the serum phosphorus level ranged from _4 to 4.8 mg/100 ml. In 18 cases from Boston the lowest value was _5 mg/100 ml, and three patients had values over 4.0 mg/100 ml.

Putkonen et al. (1965b) determined serum phosphorus in 57 patients. The mean value for the first determinations was 3.46 mg/100 ml, while the mean value for the control group was 3.77 mg/100 ml.

The difference is statistically significant. The mean value for all determinations in the sarcoidosis series was 3.57 mg/100 ml. Eight sarcoidosis patients (14 per cent) had an initial serum phosphorus value under 3.0 mg/100 ml and two had values under 3.0 mg/100 ml throughout. The tendency towards low serum phosphorus values was more obvious among the patients with chronic disease.

On comparison with the above-mentioned investigation a tendency towards low serum phosphorus values was observed in the present series. The difference between the normal control group and the sarcoidosis groups was statistically highly significant. It is striking that low values were also noted in acute cases. Serum phosphorus values under 2.8 mg/100 ml were observed in 11 per cent of all cases investigated.

Alkaline phosphatase and SGOT

Alkaline phosphatase was determined in 107 patients with sarcoidosis by the method of Bessey and Lowry (1946). A value of 2.9 B-L units was considered as the upper limit of the normal range. Higher values were noted in three cases (2.8 per cent). None of these patients showed skeletal changes, but all showed hypercalcaemia or hypercalciuria.

One patient had values ranging from 3.1 to 3.6 B-L units throughout. In this case pulmonary changes of stage III and hypercalcuria were present. In another patient, who showed splenomegaly, skin sarcoidosis and hypercalcaemia, the alkaline phosphatase values exceeded 5 B-L units (maximum 5.15 B-L units). In the third case only one elevated value was noted (3.1 B-L units). This patient had hypercalcaemia, hypercalciuria, nephrocalcinosis and pulmonary changes at stage III.

Glutamic-oxalacetic transaminase in the serum (SGOT) was determined in 104 cases (Bergmeyer and Bernt 1962). Normal values under 40 IE were noted in all.

The alkaline phosphatase values are frequently elevated in sarcoidosis. Harrell and Fisher (1939) reported this observation, but found no correlation with either skeletal or liver disease. Of nine Baltimore patients studied by Longcope and Freiman (1952) six had alkaline phosphatase values over 6 Bodansky units, and six of 15 Boston patients had values exceeding 5 Bodansky units. In these cases values over 10 units were noted four times and values over 30 units were noted twice. Cowdell (1954) in England found that 10 out of 22 investigated patients had increased alkaline phosphatase in the serum. Cummings et al. (1959) noted elevated values in 29 per cent of 78 patients and Mayock et al. (1963) in 35 per cent in a compiled series of 138 patients. Putkonen et al. (1965b) who determined alkaline phosphatase in 51 patients, observed an increase in five (10 per cent).

As compared to the above-mentioned investigations the frequency of elevated alkaline phosphatase in the serum is low in the present series, in which only three of 107 patients investigated showed an increase.

So far no correlation has been observed between increased alkaline phosphatase and changes of the bone in sarcoidosis. By contrast, changes of the liver have frequently been reported in connection with elevated alkaline phosphatase values. In sarcoidosis series in which liver biopsy has been routinely performed, as many as 80 per cent of the patients have exhibited liver lesions. Israel and Sones (1964) had 49 positive biopsies among 61 performed. It therefore seems possible that intrahepatic biliary stasis due to epithelioid cell granulomas in the liver is involved. On the other hand, patients with verified sarcoidosis in the liver have shown normal serum alkaline phosphatase (Longcope and Freiman 1952). However, it should be borne in mind that alkaline phosphatase activity may originate not only in the bone and liver, but also in the kidneys and the gastro-intestinal tract. The fact that SGOT was within the normal range in all of the present 104 investigated cases is consistent with the theory of intrahepatic biliary stasis.

CONCLUSION

The clinical picture of sarcoidosis in Finland was studied in a series of 140 patients from south and southwest Finland, whose disease was discovered during the period 1959–1967. In a study of the prevalence of sarcoidosis performed in different parts of Finland it was found that the clinical picture is uniform. Therefore, the data collected in the clinical study may be considered as representative for the whole country.

The Finnish sarcoidosis patients exhibited a typical clinical picture, which did not differ appreciably from that known from Scandinavian reports. The ratio of women to men was about 2:1, which is in agreement with the majority of earlier studies, although a different sex ratio has been reported by some authors.

As regards the age distribution, the older age groups were found to be somewhat more frequently represented than in other series from Scandinavia and other parts of the world. The age group 30–39 years was the largest, while most female patients were found in the 40–49 group. This is not accounted for by the fact that the series was collected from hospitals, since practically all patients suspected

of sarcoidosis, even in the absence of symptoms, have been hospitalized for investigation. The relative frequency of young women presenting with EN is a characteristic feature in earlier Scandinavian reports. In the present series the women presenting with EN were older which seems to indicate that sarcoidosis really commences at a later age in Finland.

The morbidity was not influenced by the environmental background of the patients. Urban cases were somewhat more numerous, but calculated on the census the distribution was found to be uniform.

About 40 per cent of the cases were asymptomatic when detected which is in agreement with earlier Scandinavian and English reports. In North American series, on the other hand considerably lower ratios of asymptomatic cases have been indicated. Sarcoidosis was more often discovered in symptomless phase in men than in women. Among the patients with symptoms the women showing EN constituted the largest group. This is in agreement with the situation in Sweden but in the present series the group was small absolutely speaking as compared to the figures reported by Swedish authors. Joint symptoms without EN and respiratory symptoms were also frequent findings. In some cases only unspecific general symptoms were observed, and a few patients presented with uveitis or involvement of the parotid gland. Surveying the whole series, it may be stated that the disease started in much the same way as has been reported from Scandinavia and England, but differently from what has been described by North American authors.

Of the patients with subjective symptoms a strikingly high proportion had fallen ill during the spring months of April and May. This was found to be due to an accumulation of cases of EN during these months. The same observation has been reported previously and is not specific for sarcoidosis. The phenomenon involved is a characteristic seasonal variation for EN irrespective of etiology.

An association between the onset of sarcoidosis and pregnancy or lactation was observed in some cases, but no so often as has been reported in Sweden. The mean age of the female patients was higher than in the reports cited for comparison. This seems to suggest that pregnancy and lactation do not primarily elicit sarcoidosis and do not themselves determine the time of onset.

The distribution of changes over the different organs is in agreement with what has previously been observed in Scandinavia and England. The majority of the patients had acute-subacute sarcoidosis with only a few organs involved. As regards the intrathoracic lesions, BHL alone was the most frequent finding, while pulmonary fibrosis in an advanced stage was infrequent. Pleural changes with effusion in the pleural space were seen in four cases. Two patients showed specific, gross changes of the bronchial mucosa, but specific microscopic changes were observed in half the cases showing unspecific or no macroscopic changes. Positive biopsy results were more often obtained in patients also showing pulmonary infiltration and in cases in which multiple biopsies were performed.

EN occurred more frequently in women than in men (4 1). The ratio was the same as in earlier nonselected Scandinavian series. Relatively speaking EN was more frequent among women of the younger age groups.

Ocular symptoms, most frequently uveitis, were observed in 10 per cent of the whole series, but in 20 per cent of the patients examined by an ophthalmologist. Similar frequency figures have been reported in Swedish and English series collected in the same way.

Specific skin lesions — sarcoidosis in scars and nodular infiltration of the skin — were seen in 6 per cent of the patients. This ratio is low as compared to earlier reports.

Specific changes of the bone were noted in 3.5 per cent of those investigated for such lesions. This figure is of the same order as those reported in Scandinavian and English series consisting predominantly of acute-subacute cases.

Renal changes of three kinds were observed in the present patients: acute interstitial nephritis in acute sarcoidosis, granulomatous changes in the renal parenchyma and nephrocalcinosis. The last-mentioned two forms were more frequent in disseminated disease, but in two patients with non-disseminated sarcoidosis showing no symptoms of renal involvement routine percutaneous renal biopsy revealed granulomas in the renal tissue.

Splenomegaly was observed in only two patients, which is a low frequency as compared to the majority of earlier reports.

Kveim's test was performed in 96 cases. A positive reaction was noted in 79 per cent. The highest ratio of positive reactions was obtained in the group with EN (96 per cent). Of the group with BHL without EN 87 per cent reacted positively. The test result was positive in 68 per cent of the cases showing nonfibrotic pulmonary infiltration. In three cases of pulmonary fibrosis no positive reaction was obtained. The frequency of positive reactions was approximately the same as in North American investigations in which the same test material was used.

Tuberculin positivity was observed in a high proportion of the patients as compared to other reports. The degree of tuberculin positivity seems to be the highest ever noted in sarcoidosis. However when the present sarcoidosis series was compared to

a normal control group from the same geographical area, an obviously lower tuberculin positivity was found in all sarcoidosis groups. This seems to be accounted for by the high frequency of tuberculosis in Finland and the general BCG vaccination.

Lymph node biopsy performed in five cases in connection with mediastinoscopy gave positive results. Biopsy of palpable nodes also proved to be useful. Biopsy performed on the prescalene fat pad by Daniels' method was positive in half the cases. Random biopsies of skeletal muscle gave positive results in four cases of 14. Specimens from other organs were taken in occasional cases showing symptoms of specific organ involvement.

A normal or moderately elevated erythrocyte sedimentation rate was observed in most cases, except in those showing EN. In these, elevation of the ESR was a frequent finding.

The serum total proteins were normal in all investigated patient groups. The albumin level was significantly decreased as compared to a control group. No differences were observed in the $alpha_1$ globulin fraction. $Alpha_2$ globulin showed an increase in all sarcoidosis groups, the maximum elevation being noted in the patients showing concomitant EN. Beta globulin was also increased, except in the group with pulmonary fibrosis. The gamma globulin fraction was elevated in all groups of sarcoidosis. The greatest increase in globulin, as compared to the normal control series, was noted in the $alpha_2$ fraction.

The latex fixation test was positive in 19 per cent of the women and 4 per cent of the men.

Hypercalcaemia over 11 mg/100 ml was observed in 9 per cent of the cases, hypercalciuria exceeding 250 mg/24 h in 17 per cent. These results corroborate previous reports that hypercalciuria occurs more frequently in sarcoidosis than hypercalcaemia. A tendency towards hypophosphataemia was found in all patient groups as compared to the normal control group although most of the values noted were within the normal range.

The clinical features of sarcoidosis in Finland were found to be the same as have previously been described in Scandinavian and English reports. The morbidity was higher in women than in men. The acute-subacute form was much more frequent than the chronic form. The ratio of asymptomatic cases was high, and EN was common. The older age groups were more frequently represented, and the ratios of Kveim positivity and tuberculin positivity were higher than in previous reports.

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About 40 per cent of the cases were asymptomatic when detected, which is in agreement with earlier Scandinavian and English reports. In North American series, on the other hand, considerably lower ratios of asymptomatic cases have been indicated. Sarcoidosis was more often discovered in symptomless phase in men than in women. Among the patients with symptoms the women showing EN constituted the largest group. This is in agreement with the situation in Sweden, but in the present series the group was small, absolutely speaking, as compared to the figures reported by Swedish authors. Joint symptoms without EN and respiratory symptoms were also frequent findings. In some cases only unspecific general symptoms were observed, and a few patients presented with uveitis or involvement of the parotid gland. Surveying the whole series, it may be stated that the disease started in much the same way as has been reported from Scandinavia and England, but differently from what has been described by North American authors.

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patients showed no radiological change after two years. In one case the condition progressed during the second year of observation. Twenty-one months after the disease was diagnosed this patient developed enlargement of previously normal paratracheal and peripheral lymph nodes. At the same time the hilar lymphadenopathy progressed. Glucocorticoid treatment was started and the condition improved but the patient was not entirely cured at the time of writing

Only nine patients have been followed up for *five years* Of these, six were completely cured and three showed obvious remission when last seen.

Summarizing, it may be stated that of the untreated patients with pulmonary changes at stage I 66 per cent were cured or showed obvious improvement during the first year of observation. The corresponding figure after two years is 91 per cent Only three patients (5 per cent) showed progression of the changes on account of which treatment was started.

Stage II The prognosis of the untreated patients with pulmonary changes at stage II appears in Fig. 24 No treatment was administered in these cases because of the subjectively good general condition and because the lung function was normal. This group comprises 32 patients. Four of these (13 per cent) were cured during the *first year* while 10 (31 per cent) showed obvious improvement and 10 (31 per cent) showed no change. Eight patients showed radiological progression during the first year and were then treated The time of observation before the administration of treatment was two months in one case four months in four cases, and five seven and nine months in one case each. In addition to impairment of the pulmonary lesions two of these patients showed other changes considered as an indication for treatment. In one case granulomas were discovered in the kidney the other showed persistent subjective joint symptoms and signs of exudative pleurisy In this group of treated cases three patients attained normal chest radiographs. One of these had a recurrence two years later but remission was again attained by glucocorticoid treatment. Four patients showed obvious improvement, while one had a severe recurrence seven months from the completion of treatment for five months. The new lesions have proved irreversible.

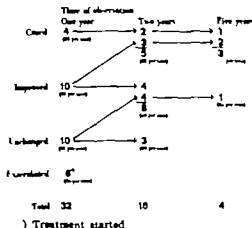


Fig 24 Prognosis f pulmonary sarcoidosis. St ge II. Primarily untreated patients.

Sixteen patients were followed up for *two years*. Five of these were cured, eight showed definite improvement and three were unchanged. No case suffered exacerbation during the second year of observation.

Only four patients in the group under discussion were followed up for *five years* Three of them were completely cured and one showed definite improvement when last seen. The small number of cases in this group is accounted for by the fact that the principle of not treating patients with pulmonary changes at stage II was only adopted during the later half of the period covered by the present study

Summarizing, it may be stated that of the untreated patients at stage II 44 per cent were cured or showed obvious improvement during the first year of observation. Of the remainder 81 per cent were cured or showed obvious improvement during the second year During the first year the condition was aggravated in eight cases (25 per cent) to such a degree that glucocorticoid treatment had to be started

Treated cases

Treatment

The treated patients have been divided into groups according to their pulmonary stage at the time of the administration of treatment. During the first half of the period covered by the present study (1959–1962) treatment was in many cases started as soon as the diagnosis had been verified. At that time consensus had not yet been attained with regard to the indications for treatment Later (1963–1967), treatment was administered only when progressive pulmonary disease with functional impairment was observed, in cases of persistent hypercalcaemia and/or hypercalciuria and in cases of extrathoracic organ manifestations possibly leading to impairment of vital functions, above all in cases of renal or ocular involvement. In a few cases treatment was given on account of persistent severe joint pain and fever

The treatment consisted of glucocorticoid medication in all cases. As a rule, treatment was given for at least three months, otherwise until a normal chest radiograph or a stationary stage was attained or a normal lung function was observed The dose which the patient had received for the longest period is regarded as the maintenance dose. In most cases the initial dose was 30—40 mg prednisolone a day This dose was successively lowered so that the maintenance dose was attained after two to three weeks treatment.

The treatment given at stage I is shown in Table XXVIII This group comprises 20 patients, 10 of whom showed only BHL and no extrathoracic manifestations. The period of treatment exceeded one year in only one case. This patient had renal sarcoidosis with impaired renal function as the most severe manifestation The shortest periods of treatment are found in the group with BHL alone. One patient was treated for a month on account of severe subjective joint symptoms. The maintenance dose was 10 mg prednisolone a day in six cases and 7.5 mg a day in another six cases. Eight patients were given 5 mg a day

Table XXIX shows the treatment at stage II. Of the 29 patients in this group 22 showed pulmonary changes as the only indication for treatment. The mean period of treatment was nine months, but in the group with pulmonary changes alone it was eight months. The period of treatment was longest (28 months) in a case of concomitant hypercalcaemia and hypercalciuria. The maintenance dose was 5 mg prednisolone a day in 10 cases, 7.5 mg a day in 11 cases 10 mg a day in six cases and 15 mg a day in two cases.

On comparing the period of treatment at stage I and stage II it is found that the average period was two months longer at stage II In the groups showing pulmonary changes alone the average period was four months longer at stage II The distribution of the maintenance doses over the two stages was uniform.

Prognosis

In this analysis of the prognosis of the treated pa

Table XXVIII. Glucocorticoid treatment in pulmonary sarcoidosis at stage I (BHL).

Indications for treatment	No of pat.	Duration of treatment		Maintenance dose Prednisone/day		
		Mean duration in months	Range in months	No of pat. 10 mg	7.5 mg	5 mg
BHL alone	10	4	2.5—6.5		3	5
Peripheral lymphadenopathy	1	12		1		
Ocular sarcoidosis		5.5	4—7		1	1
Hypercalcaemia and/or hypercalciuria	2	6.5	5—8		1	1
Renal sarcoidosis	2	23.5	8—39	1		1
Interstitial nephritis	1	5		1		
Joint pain	1	1		1		
Bone cyst and concomitant sarcoidosis of eyes and nasal mucosa	1	12			1	
Total	20	7	1—39	6	6	8

Table XXIX. Glucocorticoid treatment in pulmonary sarcoidosis at stage II

Indications for treatment	No. of pat.	Duration of treatment		Maintenance dose Prednisone day			
		Mean duration in months	Range in months	No. of pat. 15 mg	10 mg	7.5 mg	5 mg
Pulmonary lesions alone	22	8	3—19	2	4	9	7
Contributory causes.							
Hypercalcaemia and or hypercalciuria	3	16	3— 8		1	1	1
Ocular sarcoidosis	1	9					1
Renal sarcoidosis	1	8			1		
Protracted fever	1	6				1	
Joint pain and pleurisy	1	7					1
Total	29	9	3—28	2	6	11	10

tients only those who were immediately treated have been considered.

Stage I Eighteen patients showing BHL alone were treated. The development appears in Fig 25 Radiologically no cases remained static. During the *first year* 11 patients (61 per cent) were completely cured, six (33 per cent) showed improvement and one showed exacerbation. This patient was treated for eight months on account of hypercalcaemia and hypercalciuria, but after discontinuation of the treatment pulmonary infiltration developed, for which medication was started again after six months of observation. The subsequent course was favourable, but two years after the onset of illness the condition was still poorer than initially

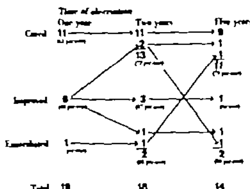


Fig 25 Prognosis f pulmonary sarcoidosis. Stage I. Patients primarily treated by glucocorticoid medication.

After an observation period of *two years* (all 18 patients) 13 patients were cured and definite improvement was noted in three. Exacerbation was observed in one patient who had shown definite signs of improvement during the first year This patient was initially treated for concomitant ocular sarcoidosis. After seven months' treatment obvious improvement was noted. After a stationary period of eight months the patient developed pulmonary infiltration corresponding to stage II. At the same time elevated calcium values were measured in the serum and urine. After treatment for 16½ months the chest radiographs were almost normal, but after another two years and eight months exacerbation occurred with severe renal changes, nephrocalcinosis and renal failure.

Fourteen patients were followed up for *five years* Of these, 11 were completely cured and one showed obvious improvement. Exacerbation occurred in one case in addition to those discussed above. The patient in question was primarily treated for five months on account of hypercalcaemia. Definite improvement was noted, and this persisted after the discontinuation of treatment so that the condition was entirely normal two years after the institution of therapy After another two years of observation typical skin manifestations and splenomegaly developed. During the course of reassumed treatment the size of the spleen was normalized and the radiological appearance of the lungs was almost normal when the patient was last seen, but the skin lesions persisted.

In summary it may be stated that in 17 of the 18 patients in this group (94 per cent) the development was favourable during the first year healing of lesions or obvious improvement being noted. The same is true for 16 patients (89 per cent) followed up for two years. Three patients (17 per cent) showed signs of exacerbation at one stage or other of the observation period. One of these was completely cured by protracted treatment.

Stage II Twenty-three patients with pulmonary changes corresponding to stage II at the time of diagnosis were treated with glucocorticoids. The development appears in Fig 26. During the *first year* eight patients (35 per cent) were completely cured and 13 (56 per cent) improved. Exacerbation was noted in two cases. In one of these, primary treatment for 6½ months was successful, but at the end of the first year of follow-up new lesions developed, which resolved under resumed medication. After an observation *period of five years* the patient s condition was normal. In the other case fibrotic pulmonary changes corresponding to stage III and skin lesions developed in spite of continuous treatment. After 30 months treatment the situaiton was unchanged.

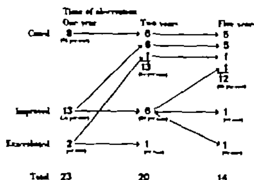


Fig 26 Prognosis of pulmonary sarcoidosis. Stage II. Patients primarily treated by glucocorticoid medication.

Twenty patients were followed up for *two years* Of these, 13 were cured (65 per cent) and six (30 per cent) showed improvement. No exacerbation was noted during the second year

In 14 cases the time of observation is *five years*

Twelve of these patients were cured, one was improved, while the condition was aggravated in one case. This patient had a recurrence three years after the discontinuation of successful treatment. After this initial period of treatment slight, stationary parenchymatous changes persisted and the pulmonary function was normal When the recurrence occurred, exudative confluent pulmonary infiltration was first observed, but this soon changed into a fibrotic stage, which has proved resistant to treatment. The patient showed moderate restrictive ventilatory insufficiency when last seen.

Summarizing, it may be stated that treatment gave favourable results in 91 per cent of cases after one year and in 95 per cent after two years. In three cases the development of the disease was unfavourable but one of these patients was cured by resumed treatment.

No difference was observed on comparing the prognosis of the untreated patients at stage I with that of the treated patients at the same pulmonary stage During the first year of observation more rapid improvement was seen in the treated group, but after two years the results were similar In the untreated group 91 per cent of the patients were cured or showed obvious improvement, while the corresponding figure for the treated group is 89 per cent.

Likewise, after one year the results were definitely better in the treated group at stage II, but after two years the difference was reduced so that the proportion of cures or obvious improvements was 81 per cent in the untreated group against 95 per cent in the treated group. However the number of patients in both groups is so small — 16 and 20 respectively — that no conclusion can be drawn except that the prognosis was good in both groups.

Since at pulmonary stages I and II the prognosis does not seem to be influenced by treatment the treated and untreated groups were united in Table XXX for analysis of the effect of EN and extrathoracic changes on the prognosis. In this analysis the course during the first two years is considered.

Stage I As may be seen in the table, the patients with EN had the best prognosis. After one year of observation, aggravation of the condition was seen in two cases, but after two years all patients were cured or showed definite improvement including two cases in which exacerbation was observed after one year Of the patients showing BHL alone one of 31 showed exacerbation after one year and the condition still was poorer than initially after two years of observation. Three patients showed no change and 21 showed obvious improvement or complete healing Of 10 patients with extrathoracic manifestations nine were followed up for two years. In two of these the condition was aggravated. Summing up, after two years observation only one patient of 57 without extrathoracic changes showed exacerbation, while this was true of two out of nine with such manifestations.

Stage II The patients at stage II with EN also showed a favourable development. There were only six such cases, but during the first year of observation no impairment occurred, and after two years none of the remaining four was unchanged or showed exacerbation. Of the patients with pulmonary infiltration as their only manifestation of the disease, seven were impaired during the first year All these cases were followed up for two years. It is noteworthy that after two years only one patient of 31 showed exacerbation. Of the patients with pulmonary infiltration and concomitant extrathoracic changes three of nine showed progression of the disease during the first year The period of observation is two years in only one of these cases. Of seven patients followed up for two years one showed a poorer condition than initially In the group without

Table XXX. Prognosis of pulmonary sarcoidosis at stages I and II with and without extrathoracic organ manifestations.

	Time of observation One year					Two years				
	Total	Cured	Improved	Unchanged	Exacerbated	Total	Cured	Improved	Unchanged	Exacerbated
Stage I										
BHL + EN	36	15	1	7	–	32	22	10	—	—
BHL alone	31	8	12	10	1	25	15	6	3	1
Extrathoracic manifestations	10	3	6	1	—	9	5		—	2
Stage II										
with EN	6		3	1	—	4			—	—
without EN	40	8	17	8	7	31	15	13		1
Extrathoracic manifestations	9		3	1	3	7	3	2	1	1

extrathoracic manifestations one patient of 35 showed exacerbation after two years, against one of seven in the group with such changes.

Summarizing, it may be stated that the patients with pulmonary changes at stages I and II and concomitant EN had a very good prognosis, and that the patients with similar lung changes without EN had a better prognosis when no extrathoracic changes were present. Relatively speaking, an unfavourable course was most frequent among the patients who showed extrathoracic organ manifestations.

STAGE III

Eight patients showed pulmonary changes corresponding to stage III at the time when they were included in the present series. In five cases the diagnosis of sarcoidosis had been made previously at another hospital. All of these eight patients also showed extrathoracic manifestations of sarcoidosis. The period of observation after pulmonary lesions at stage III had been diagnosed was seven years in one case five years in two, four years in one, three years in two and two years in two cases.

No treatment was given in two cases in which the lung lesions were stationary and the lung function only slightly reduced. Six patients received treatment All of these showed extrathoracic organ manifestations. The maintenance dose did not exceed 10 mg prednisone daily Treatment was discontinued after seven months in one case, after 1½ years in one and after two years in two cases. Of two patients still under treatment one has received continuous medication for over four years, the other for over one year One patient who died had been treated for four years. Some improvement of ventilation was observed in two cases after seven and 18 months respectively when these patients were last seen. Three patients show exacerbation in spite of treatment. Two of these have developed nephrocalcinosis and renal insufficiency while the third patient shows progressive pulmonary infiltration. The patient who died showed very severe respiratory failure and chronic cor pulmonale. The immediate cause of death was acute respiratory infection. Radiologically the pulmonary lesions had then been stationary for four years.

Summarizing, it may be stated that the pulmonary lesions have proved irreversible in patients showing stage III. However improvement of ventilation was attained in two cases.

DISCUSSION

The available data concerning the prognosis of sarcoidosis vary Schaumann (1936), who called the disease lymphogranulomatosis benigna did not regard the prognosis as good the term benigna only meant that the general condition was relatively unaffected and the course protracted. Bruce and Wassén (1940), on the basis of seven cases followed up, stated that the prognosis may be considered good as far as mortality and rehabilitation are concerned. King (1941) described 37 cases, half of which were biopsy-proved. In 23 cases the pulmonary lesions healed completely or almost completely within three years. Three patients showed improvement and eight showed no change after observation periods ranging from three months to four years, and three patients showed aggravation of the condition Reisner (1944) in New York published the results of a five-year follow-up study of 28 patients. Nine showed improvement, five were unchanged and five showed healing of some lesions and progression of others, while in nine cases the disease had steadily progressed. Seven of these patients had died. Reisner concluded »The prognosis depends largely on the extent of persistent organic changes and on the degree of permanent functional damage resulting from localization of the lesions in particular organs.» Lovelock and Stone (1953) reported the results in a series followed up in part for 3½ years. Twelve patients had been treated with cortisone or ACTH and these were compared to 27 untreated patients. The pulmonary lesions healed in 64 per cent in the treated group against 44 per cent in the untreated group. Fagerberg (1953) studied a Swedish series consisting of 54 patients. Initially 10 showed only BHL, 28 showed BHL and pulmonary infiltration and eight had normal chest radiographs. Ten patients showed EN eight had ocular manifestations of sarcoidosis. The series was collected during the years 1944—1951 and a follow-up investigation was performed in 1951 The period of observation was therefore short in many cases. At follow-up it was found that six patients had died and six showed considerable exacerbation. Thirty-three patients exhibited lesions in one or more organs and none of these was subjectively in good health. Only 10 patients felt subjectively well. Fagerberg concluded that the prognosis in sarcoidosis cannot be considered as good.

Löfgren (1953 b) found that the prognosis in »primary pulmonary sarcoidosis» is good. Of 212 patients half were followed up for two to three years, half for three to 16 years. No specific treatment was administered. Twenty-eight patients (13 per cent) also showed parenchymatous changes when the diagnosis was made, and another 53 (25 per cent) later developed pulmonary infiltration. In the group with EN (111 cases) complete resolution was observed within one year in 64 per cent and within two years in 92 per cent. In nine cases (8 per cent) the parenchymatous lesions showed signs of progression and

tended to become chronic. In 62 asymptomatic cases the disease had been discovered by mass chest radiography In this group the course was somewhat less favourable than in the group with EN. Complete healing was observed in 47 per cent after one year and in 73 per cent after two years. Seventeen patients (?7 per cent) showed a chronic trend. In the group of miscellaneous cases the distribution of the results was the same as in the asymptomatic group.

Carr and Gage (1954) analysed a series of 194 patients whose disease had been diagnosed at the Mayo Clinic in 1940–1951 Only nine patients were negro These authors wrote as follows: »More than 90 per cent of the patients were traced, and the five-year and ten-year survival rates were found to be 92.9 per cent and 80 per cent, respectively There was no evidence that the prognosis was influenced by age, sex, race, tuberculin sensitivity of the patient or the treatment administered.»

Cowdell (1954) in Oxford, England, described a series of 90 patients with an observation period of less than two years in 19 cases, two to 10 years in 44 cases and over 10 years in 27 cases. Seventeen patients died, eight of sarcoidosis. At follow-up investigation 39 patients (43 per cent) felt subjectively well and had no demonstrable lesions, 22 (24 per cent) showed improvement, 10 (11 per cent) were unchanged and two showed exacerbation. Cowdell stated that »sarcoidosis is usually a relatively innocuous condition, although involvement of certain organs or systems, notably the lungs, heart eyes, and central nervous system, may have serious or fatal results. The tendency to spontaneous remission, which may affect the assessment of therapeutic results, is emphasized.»

Israel and Sones (1958) described a North American series consisting of 160 patients, 138 of whom were negro. They noted a mortality of 8 per cent. Two patients died of tuberculosis, 11 of progressive sarcoidosis. Complete clearing of symptoms and radiological changes was observed in 34 per cent and an additional 27 per cent were classified as improved

Hedvall (1960) studied 14 untreated cases diagnosed during the years 1941–1958. The period of observation ranged from eight months to 15 years. Forty patients had EN Of these, 33 were completely cured, five showed improvement although slight changes persisted, and two with a short follow-up time were unchanged. In the group of 102 patients without EN 19 showed BHL alone 14 showed BHL and mediastinal adenopathy while in one case only the mediastinal nodes were enlarged. Thirty-three patients had BHL and or mediastinal adenopathy and pulmonary infiltration, 35 showed only pulmonary infiltration. Complete healing was observed in 48 cases, and in ?0 only slight changes persisted. Another 13 patients showed improvement, although marked changes were still noted when the patients were last seen The findings were unchanged in six cases, and exacerbation was observed in 15

Scadding (1961) assessed the prognosis on the basis of 136 cases classified as follows: Group 1 32 patients, enlarged hilar lymph-nodes only Group 2, 40 patients, mottled shadowing in the lungs with enlarged hilar lymph-nodes, either present or known to have been present in the past. Group 3 37 patients, mottled shadowing in the lungs, without present or available past evidence of enlargement of hilar lymph-nodes. Group 4 27 patients, radiographic and clinical features suggesting fibrosis, usually in addition to mottled shadowing. Scadding also studied the effect of corticosteroid treatment on the prognosis and found that this may depress both subjective symptoms and manifestations in reversible stage but he maintained that after discontinuation of treatment the disease assumes the form it would have had without treatment. According to Scadding, corticosteroid treatment in sarcoidosis is only suppressive and does not influence the prognosis.

In Scadding s series the prognosis was as follows: In group 1 84 per cent had normal chest radiographs after five years and 97 per cent were symptom-free. In group 2 53 per cent of the patients had recovered, 5 per cent showed slight radiological changes but were symptom-free 28 per cent showed mild symptoms and radiographic evidence of slight changes in the lungs, while in 7.5 per cent disabling symptoms were present. One patient had died of a cause other than sarcoidosis. In group 3 43 per cent had attained radiographic resolution, 16 per cent had some residual changes with no disability 22 per cent had residual changes with slight disability and 16 per cent had moderate disability One had died of an unrelated cause. In group 4 six patients died of pulmonary fibrosis due to sarcoidosis. One died of an unrelated cause. Of the remaining 20 10 remained unchanged, seven showed some improvement and three became worse during the five years observation. An onset with EN was found to be associated highly significantly with a good prognosis.

In a study of 204 confirmed cases of sarcoidosis Rudberg-Roos (1962) found that the prognosis was dependent on the way in which the disease commenced. The most rapid resolution of BHL was noted in »acute cases among which 90 per cent showed complete healing within two years. Among »probably early cases» healing was observed within one year in 35 per cent, within two years in 40–50 per cent, within three years in 60 per cent, and after more than three years in 80 per cent. Among »probably not early cases» no tendency towards resolution

was seen within five to 10 years. Healing of parenchymatous lesions occurred in the same proportion of cases as BHL, but the course was more protracted. Persistent parenchymatous changes were noted in 10 per cent among »acute cases» in 30 per cent among »probably early cases» and in 70 per cent in »probably not early cases» Ten patients died during the period of observation. The cause of death was sarcoidosis in five, or possibly six, of these.

Moriyama (1961) assessed the mortality in sarcoidosis in the U.S.A. on the basis of data obtained from the National Office of Vital Statistics, U.S. Public Health Service. He found that the mortality had doubled during the period 1949—1958 from 0.5 to 1.0 per 1 million of population. For whites, the mortality was insignificant in the age groups below 25—34 A slight rise was then observed, and the peak was seen at the age of 70 For the coloureds, a significant mortality was noted 10 years earlier than for the whites, and the peak was reached at the age of 40 for women at the age of 30

Douglas (1964) discussed the prognosis of early sarcoidosis in Scotland. Among 86 patients with BHL, spontaneous remission occurred in 79 per cent within one year and in 89 per cent within two years. Thirty-nine per cent had presented with EN All these patients belonged to the group showing complete healing When nine patients (11 per cent) with persistent BHL were discounted, no difference was observed in regard to the development in the groups with and without EN Mandi (1964a) in Hungary also found that the prognosis in early sarcoidosis was good. His series comprised 78 cases of early sarcoidosis, 14 of which showed EN He observed no difference in prognosis between the groups with and without EN Stavenow (1964) analysed the prognosis of 44 Swedish patients with acute or subacute sarcoidosis without EN and compared the results with those obtained in earlier Swedish series of EN patients. He found that the prognosis was good in both acute cases (healing within one year in 58 per cent within two years in 80 per cent) and subacute cases (healing within one year in 36 per cent, within two years in 59 per cent) No statistically significant differences were observed between these groups and earlier reports of EN series.

As appears from the reports cited above, views concerning the prognosis of sarcoidosis have varied during the course of time and even now no consensus has been attained. It is obvious that the prognosis of negro patients is poorer than that of whites. Moreover it has clearly appeared that the prognosis in early sarcoidosis is good, since 80 to 90 per cent of patients are completely cured within two years. Cases presenting with EN seem to have an especially good prognosis. EN is a readily recognized feature, typical of the onset of acute sarcoidosis. In patients with early sarcoidosis without EN it is often a problem to establish the precise time of onset. It is therefore possible that the difference in prognosis between early cases with and without EN observed by some authors is due only to a difference in duration of the disease. The prognosis in cases of non-fibrotic pulmonary changes also seems to be good, although not as good as at stage I. The process of healing moreover requires a longer period of time. When fibrotic changes have developed in the lung parenchyma the prognosis is poorer Complete resolution no longer occurs, and a large number of patients are permanently disabled because of respiratory insufficiency The mortality among whites is not high. The majority of patients with present or past sarcoidosis die of some other cause.

Before the era of corticosteroid therapy various methods of treatment were tried in sarcoidosis without success. At the Second International Conference on Sarcoidosis, Washington D C., 1960 it was stated that the »administration of corticosteroid hormones is the only method of drug treatment which is now known to be of some value» The following indications for treatment were agreed upon. 1 Active ocular disease. 2. Progressive pulmonary involvement, as evidenced by increasing symptoms or roentgenographic changes, or impaired or deteriorating pulmonary function. 3 Persistent hypercalcaemia or hypercalciuria. 4 Central nervous system involvement with significant functional impairment. 5 Disfiguring cutaneous lesions. 6 Myocardial sarcoidosis. These indications are still valid. Corticosteroid treatment has proved valuable particularly in cases of extrathoracic involvement. In patients with pulmonary lesions the symptoms are depressed and the radiographic changes are more rapidly resolved, but the medication is not curative, and most authors are agreed that it does not influence the prognosis of the pulmonary process.

Later other drugs have also been tested in the treatment of sarcoidosis. Chloroquine has proved valuable in skin sarcoidosis (Morse et al. 1961 Siltzbach and Teirstein 1964). A suppressive, but not curative, effect has also been observed in pulmonary sarcoidosis (Morse 1967). James et al. (1967), who compared the effect of prednisolone, oxyphenbutazone and placebo after six months treatment obtained significantly better results with the two drugs than with placebo The results with the different drugs were similar It is noteworthy however that this study was only concerned with the initial phase of the disease.

CONCLUSION

In sarcoidosis at stage I the prognosis was found to be good, especially in cases presenting with EN. When corticosteroid treatment was administered, resolution of the lesions was more rapid during the first year but at the end of the second year no significant difference was observed. The prognosis may also be considered good at stage II, although not as good as at stage I. Spontaneous healing of the lesions required a longer period of time, and the difference between the untreated and treated cases was therefore more marked after one year of observation. After two years the difference between the groups was slight. It thus appeared that at stages I and II the prognosis was not appreciably influenced by treatment. In those cases in which initial pulmonary changes showed marked progression corticosteroid medication seemed to depress the subjective symptoms and, perhaps, prevent the development of irreversible fibrosis. In the presence of pulmonary fibrosis the radiological development was not influenced by treatment.

The patients showing extrathoracic organ manifestations had a poorer prognosis.

Considering that Finnish patients with sarcoidosis usually show stages I and II the prognosis of this disease in Finland must be assessed as good.

VI. GENERAL SUMMARY

The purpose of the present study was to estimate the frequency of pulmonary sarcoidosis and to describe the clinical picture and assess the prognosis of this disease as it appears in Finland. From the results obtained the following conclusions may be drawn:

1. The frequency of pulmonary sarcoidosis in Finland

A prevalence investigation performed on the basis of mass radiographic surveys in 12 tuberculosis dispensary districts in 1962–1967 (1.5 million radiographs) revealed a prevalence of verified pulmonary sarcoidosis of 7.5 per 100,000 radiographs. A local variation occurred, but this could not be correlated to the tuberculosis situation.

An incidence investigation performed in the same 12 districts in 1962–1967 revealed an incidence of sarcoidosis of 5.3 new cases annually per 100 000 of population. The same local variation was observed as in regard to the prevalence, the highest incidence (9.1 per 100,000) being noted in the tuberculosis district of Raseborg. No correlation with the situation in regard to tuberculosis was found.

A survey of the patients with sarcoidosis admitted to Finnish hospitals in 1960 and 1967 gave a figure of 55 new cases in 1960 and 220 in 1967. Considering the results of the prevalence and incidence investigations it cannot be stated, however that the frequency of pulmonary sarcoidosis has increased. It is obvious that the figure for 1960 is much too low.

Calculated on the census the annual number of new cases of pulmonary sarcoidosis in Finland is 220–240.

2. The clinical picture of pulmonary sarcoidosis in Finland

The clinical picture of sarcoidosis in Finland was studied in a series of 140 patients. Since these exhibited the same clinical features as the patients on whom the frequency investigations were performed, the results are valid for the whole country. On comparison with earlier reports from other countries, sarcoidosis in Finnish patients was found to be a disease of very much the same nature. The ratio of women to men was about 2.1. The 30–39 age group was most frequently represented, but among the women the 40–49 group was the largest. Forty per cent of the patients were symptom-free when their disease was discovered, while 60 per cent sought medical advice on account of subjective symptoms. Among those showing symptoms, women with EN constituted the largest group.

The majority of cases were of the acute-subacute type with involvement of only a few organs. BHL was the most frequent radiographic finding. Pulmonary fibrosis in an advanced stage was rarely seen. Ocular manifestations were observed in 10 per cent, skin lesions in 6 per cent and changes of the bone in 3.5 per cent.

The Kveim reaction was positive in 79 per cent of the patients tested. Of those with EN 96 per cent reacted positively. In the group showing non-fibrotic pulmonary infiltration 68 per cent had positive Kveim tests. The degree of tuberculin positivity was strikingly high among the sarcoidosis patients, but as compared to a normal control group the reaction was depressed in all groups.

Deviations were seen in the electrophoretic pattern of the serum proteins. The albumin level was decreased in all groups and the $alpha_2$, beta and gamma globulins showed an increase. The most notable increase was seen in the $alpha_2$ globulin fraction.

Hypercalcaemia was observed in 9 per cent, and hypercalciuria in 17 per cent of the cases. A tendency towards hypophosphataemia was seen in all groups. The latex fixation test was positive in 19 per cent of the women and 4 per cent of the men.

The results are discussed against the background of data reported from other countries.

3. The prognosis of pulmonary sarcoidosis in Finland
The prognosis of pulmonary sarcoidosis was assessed in the same series of 140 cases on which the clinical study was based. Different pulmonary stages and treated and untreated patient groups were separately analysed.

The prognosis was found to be good at both stage I and stage II. This was true of both treated and untreated patients. Glucocorticoid treatment had a depressive effect on the symptoms of the disease but did not influence the end result. Patients with extra thoracic organ manifestations had a poorer prognosis than those with pulmonary changes alone.

Since Finnish patients predominantly show acute-subacute sarcoidosis with pulmonary changes corresponding to stages I and II, the prognosis of pulmonary sarcoidosis in Finland must be considered good.

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Contents

Abstract

The relationship between the levels of urinary glucose and the viable counts of bacteria in the urine was studied in 3,911 subjects: 948 4-year-old children of both sexes, 511 schoolgirls 7 to 18 years old, and 2 452 females 7 to 65 years old, comprising 80 per cent of the total female population in this age group in a small community.

Urinary glucose was determined by the hexokinase and glucose-6-phosphate-dehydrogenase method and by a test paper Uriglox® that is sensitive to the small amounts of glucose normally present in the urine.

Subnormal levels of urinary glucose less than 2.0 mg per 100 ml, were regularly associated with significant bacteriuria. Significant bacteriuria has been defined as the growth of organisms of the same species in excess of 100 000 per ml in repeated samples. The confidence level of two consecutive cultures with these findings in predicting persistent bacteriuria was 98 per cent whereas the confidence level of a single specimen with growth of more than 100 000 organisms per ml was only 39 per cent.

The reliability of the glucose method —in one test—to detect subjects with persistent bacteriuria was 96 per cent. The reliability of the glucose method to discriminate subjects without bacteriuria was above 99 per cent.

The glucose method also discovered cases with true bacteriuria that were not detected by the conventional bacteriological technique for culture or should have been disregarded as due to commensals: one subject was found with bacteriuria due to L-forms while another had severe renal damage and growth of achromobacter that was apparently multiplying within the urinary tract above the urethra.

Special attention was given to subjects who repeatedly presented obviously contaminated specimens, and also to the possibility of low-grade growth reflecting true bacteriuria. Contamination, irrespective of its amount, was not found to influence the glucose levels. The urinary glucose seemed in no instance to be affected by low-grade growth, and the glucose values remained at the same level as found when no growth was obtained from the subject under consideration.

The results have shown that the glucose method is a valuable complement to the quantitative bacteriological method in differentiating contamination from bacteriuria.

The Uriglox® test paper was shown,

in a randomized population, to give results in agreement with the quantitative glucose method. The method requires strictly standardized procedures for the collection of the urine specimens. The instructions were followed by more than 97 per cent of the participants. Thus the glucose method offers a simple quick means for mass detec tion of bacteriuria It has a sensitivity and specificity so far not obtained with other chemical methods for detection of bacteriuria

Introduction

Bacterial infections of the urinary tract frequently appear with minimal symptoms. Early detection before manifest disease is therefore of importance. Bacteria cultured from the urine may however be only indigenous parasites that normally colonize the distal part of the urethra. In order to differentiate contamination from bacteriuria the concept of significant bacteriuria, was introduced by Kass 1956 1957 (20 21). The basis of this concept rests on the hypothesis that the number of bacteria in a series of samples from the same individual when due to contamination will vary between few and many in a randomized fashion. The characteristic of true infection, significant bacteriuria, is that *repeated* cultures show more than 100 000 organisms per ml of urine. The diagnostic difficulties have led to the search for different methods.

Chemical methods such as the Griess test (19 8) the triphenyl tetrazolium chloride (TTC) test (45) and the catalase test (2), that hitherto have been in use all have a low reliability for detecting cases of bacteriuria about one-fourth are missed (for review see Norden and Kass 1968 (35)) In 1967 Scherstén and Fritz (40) presented a new chemical method for the screening of bacteriuria. It was based on the observation by Scherstén (39) that normal urine contains small amounts of glucose that decreases in bacteriuria. The urinary glucose levels in morning samples collected from bacteriurics were found to be reduced from the normal range of 2 to 20 mg of glucose per 100 ml to below 2 mg per 100 ml. A test paper with high sensitivity to glucose was developed that could differentiate between urinary glucose levels above and below 1.5 to 2.0 mg per 100 ml (42)

The main purpose of the present investigation was to check the relationship between the levels of urinary glucose and the viable counts of bacteria. As the method requires close attention to a standardized technique for urinary sampling, the efficiency of the method in population screening was tested.

Clinical material

4-year-old children

The 4-year-old children were studied for bacteriuria as part of an extensive health control (29) The 449 girls and 499 boys comprised about 95 per cent of this age group in the city of Lund.

Schoolgirls

All girls at an elementary school, the Järnåkra school in Lund, were invited to participate. The 511 that participated 7 to 18 years old, represented 99 6 per cent of the female student body

Population study

The total female population in Dalby a small community in southern Sweden six miles east of Lund, were invited to participate in the health control. The screening for bacteriuria was initiated in September 1968 The material for the presented study represents results collected up to September 1969 Out of

Fig 1 Percentage distribution of attendants in the screening program in different age groups and according to civil status.

the 3 046 females, 2,452 (80.5 %) were examined during this period. The age distribution (Fig. 1) of those taking part in the screening did not significantly differ from the age distribution of the total female population in the community. The attendance of married women, 84 per cent was higher than that of the unmarried, 75 per cent ($p < 0.05$). Among those participating, 115 were pregnant

Methods

Principles

The concentration of glucose in the urine is influenced by the level of glucose in the plasma, glomerular filtration tubular reabsorption of glucose and by diuresis (44 36) In bacteriuria, glucose is consumed by the bacteria mainly in the urinary bladder To obtain a relevant decrease of the urinary glucose level in bacteriurics, the time necessary for incubation of the bacteria *in the bladder is 4 to 6 hours* (40) A shorter incubation time 2 to 3 hours or less, does not appreciably affect the level of urinary glucose and the concentration remains within the range of nonbacteriurics (43) During the phase preceding bacterial multiplication, the lag phase no measurable consumption of glucose occurs in vitro During the following period of maximal bacterial growth, the logarithmic phase the glucose content rapidly disappears (43) A strictly standardized procedure for the collection of the urine specimen is therefore a prerequisite when subnor *mal levels of urinary glucose are used* as the indicator of bacteriuria.

Collection of urine specimens

The participant was instructed to urinate on going to bed. This urine was discarded, but the time was recorded After this the participant was not allowed to eat anything, but was allowed to drink up to one glass of water—not milk or juice—during the night. Instructions were given not to urinate until the morning in order to ensure a retention time of at least 4 to 6 hours The sample was taken at home from the first urination in the morning In the 4-year-old group of children and in the schoolgirls, the specimens were taken as a mid-stream specimen without prior periurethral cleansing In the population study the participants were instructed to separate the labia and to clean the perineum three times from front to back with dry gauze swabs. Then, while still holding the labia apart, *the first part of the stream* was voided and part of the remainder col lected directly in the sterile test tube The samples were immediately chilled in plastic bags with ice from the refrigerator and the time was recorded. The interval between the last micturition in the evening and the first one in the morning was designated as the incubation time. The ice bag was kept in the refrigerator in the participants home until it was taken to the laboratory during the course of the day How the instructions were followed was

noted in detail for the 4-year-old children and the schoolgirls both by the parents and the nurses. In the population study only the incubation time and how the urine samples had been chilled were recorded.

Chemical procedures

A semiquantitative determination of the normal and subnormal concentrations of glucose in the urine was made with a test paper described by Scherstén et al. 1968 (42). A blue or bluish-green color reaction was considered as normal, and no color reaction, as pathological and suggesting bacteriuria In the population study faint color reactions were also registered. Quantitative determination of the urinary glucose concentration in the 4-year-old children and schoolgirls was performed with an enzymatic, fluorometric technique described by Scherstén and Tibbling (41). In the population study these determinations were performed with the same enzymatic method in conjunction with a spectrophotometric technique (Glucose UV test Boehringer) In the 4-year-old children and in the schoolgirls all urine specimens were subjected to quantitative glucose determinations, whereas in the population study only those specimens giving no color or a faint color reaction with the test paper were determined. In pregnancy however the urinary glucose concentrations were regularly determined.

The creatinine concentration was determined with the Technicon AutoAnalyzer as routinely performed at the Department of Clinical Chemistry University Hospital of Lund.

Estimation of the renal concentration capacity was performed after withdrawal of fluid and fruits for 15 hours The osmolality of the urine was determined by freezing-point depression by employing a Knauer osmometer

The excretion rate of white blood cells (WBCs) per hour was determined from 12-hour urine specimens.

Th test paper Uriglox® was supplied by AB KABI Stockholm 30, Sweden.

Bacteriological procedures

The bacteriological cultures were made on blood agar Using the calibrated loop technique the substrate was inoculated with 0 01 ml of undiluted urine and with 0 01 ml of urine diluted to 1 100 in saline (16)

The viable count and the typing of the microorganisms were made after incubation at 37°C for 16 to 20 hours The counts of colony-forming microorganisms per ml of urine were summarized as no growth or with regard to each strain, as "less than 10^3 10^3 to 10^4 or more than 10^4 respectively Results described as no growth permitted up to about 100 viable organisms per ml of urine. Slow-growing organisms might be missed. Urine containing less than 2 mg of glucose per 100 ml collected according to the instructions and giving no bacterial growth was recultured for 48 hours In such cases, cultures were also made for bacterial L forms (33)

The microorganisms were classified according to methods described by Cowan and Steel (7) Enterobacter

species however were designated as coliforms *Significant bacteriuria* was considered to be present when two samples collected consecutively showed growth of the same genus and with a viable count of more than 100 000 organisms per ml of urine

Follow-up procedure

In the 4-year-old children and schoolgirls, all cultures showing growth of any organism considered to be pathogenic for the urinary tract e g *Enterobacteriacae* enterococci staphylococci and *Pseudomonas aeruginosa*, led to the collection of new samples In the population study only cultures showing growth of more than 10^5 organisms per ml considered to be pathogenic to the urinary tract motivated the collection of new samples Generally repeated samples were collected until two consecutive urinary cultures yielded no growth. All 4-year-old children and schoolgirls with a history of urinary tract infections or presenting symptoms at the time of screening were studied two or more times irrespective of the laboratory results. In all cases in which the urine specimen showed less than 2 mg of glucose per 100 ml or the test paper gave no color reaction another sample was requested.

Results

Effectiveness of the instructions for collection of the urine specimens

Incubation time within the bladder The median incubation time for the 4-year old children and schoolgirls was around 10 hours and between 8 to 9 hours in the population study Among the 4-year old children, 920 (97 1 %) had an incubation time of more than 4 hours and in 883 (93 1 %) it was 6 hours or more All the schoolgirls had an incubation time of 4 hours or more and in 509 (99 6 %) it was 6 hours or more The distribution of the incubation times in the population study is shown in Fig. 2. The incubation time was recorded for 2,427 of the 2,452 females and in 2,391 (98 5 %) it was 6 hours or more The subjects with an incubation time of less than 6 hours were uniformly distributed according to age

Significant bacteriuria was not found in any of the subjects that had not followed the instruction of at least 4 to 6 hours of incubation of urine in the bladder when new samples collected with adequate attention to the instructions were investigated. Thus, there was no evidence that asymptomatic, significant bacteriuria was accompanied by more frequent voiding than by those without bacteriuria.

Fasting instructions. The instruction to fast during the night was followed by 507 (99.2 %) of the schoolgirls and by 934 (98.5 %) of the 4-year-old children (Table I) In all, 18 children had not fasted. In 17 of these children the glucose concentration was in the range of 2 0 to 20 mg per 100 ml, and in one 30 mg per 100 ml This girl had had one glass of fruit juice and had eaten a sandwich 30 minutes before voiding

Restriction of fluid intake The restriction of fluid intake was followed by all but eleven 4-year-old children. Of these 11 subjects five had normal glucose levels three had 1.5 to 1 9 three had 1 0 to 1 4 and none had below 1 0 mg per 100 ml of urine Of the five subjects with normal levels of urinary glucose all but one had no growth This subject showed 10^3 to 10^4 *Escherichia coli* Two new samples gave normal glucose values and no growth. The concentrations of urinary glucose were less than 2.0 mg per 100 ml in the samples from six of the 11 subjects; the bacteriological cultures gave no growth in five and "less than 10^3" in one Eight new

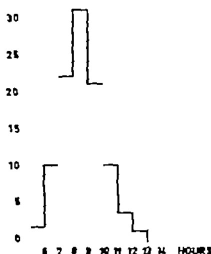


Fig 2 Distribution of the retention time of urine in the bladder in 2,427 females between the ages of 7 and 65 years.

samples collected under appropriate conditions from these six children, gave normal findings The results indicate that the low glucose values obtained from children who had not restricted their fluid intake presumably were due to increased diuresis.

Micturition directly into the test tube The instruction to micturate directly into the test tube was followed by 908 (95 8 %) of the 4-year-old children and by 510 of the 511 schoolgirls. In all, 41 samples had not been collected directly into the test tubs. In four (10 %) of the 41 samples there were more than 10^5 organisms per ml of urine The urinary glucose concentrations in these four samples were 1 6 4 0 5 7 and 7 1 mg per 100 ml. These four subjects had a heavy growth of a mixed flora An additional 13 samples were collected under appropriate conditions. In eight of these 13 samples there was no growth, in one "less than 10^3" and in four 10^3 to 10^5 The urinary glucose concentration was normal in all of them. In 36 samples that were not collected directly into test tubes the glucose concentrations were normal. The remaining subject out of the 41 had no detectable glucose and "less than 10^3" of urinary nonpathogens. The pH of this urine was 10. She had micturated in a chamber pot cleaned with sodium carbonate, which might have destroyed the urinary glucose. A new sample collected from this girl showed a normal glucose level and no bacterial growth.

Samples chilled All 511 schoolgirls returned their samples chilled. Of the 948 4-year-old children 93 (10 %) did not

Table I. Effectiveness of the instructions for collection of the urine specimens

Instruction	4-year-old children		School-girls	
	N	Per cent	N	Per cent
Fasting	934	98 6	507	99 2
Thirsting	937	99	511	100
Micturition directly into the test tube	908	95.8	510	99 8
Urine sample chilled	855	90 2	511	100
Total number and percentage following the instructions in all respects	788	83	505	98.9

return the urine sample in an ice bag; most of these 93 samples were received at the dispensary office within three hours after micturition. Four of these 93 samples showed more than 10^5 organisms per ml of urine: one had growth of *E. coli*, one had *Proteus mirabilis*, one had coagulase-negative staphylococci, and one had heavy growth of a mixed flora. The urinary glucose concentrations in these four samples were 0.4, 9.2, 6.0 and 4.4 mg per 100 ml respectively. When additional samples were collected under appropriate conditions from these four subjects, none were shown to have significant bacteriuria. Among the remaining 89 subjects who did not chill their samples there was no one, on the basis of new samples, that was found to have significant bacteriuria.

Thus, in the material of 4-year-old children and schoolgirls, 166 out of 1 459 had not followed the instructions. Out of these, 104 had "no growth", 19 "less than 10^3", 35 "10^3 to 10^5", and eight "more than 10^5". Out of the 61 subjects not following the instructions in the population study, 34 had "no growth", 14 "less than 10^3", nine "10^3 to 10^5" and four "more than 10^5". In none of these 61 subjects or the 166 children was significant bacteriuria demonstrable in additional samples.

Normal range of urinary glucose in 4-year-old children and in schoolgirls

Urinary glucose concentrations in 4-year-old children and schoolgirls with "no growth" who had followed the instructions in all respects are presented in Fig. 3. Among the 4-year-old children 564 (70 %) had no growth and in the schoolgirls 338 (67 %) had no growth. The distribution curves were slightly skewed to the right, and the coefficient of variation was 39 per cent for the 4-year-old children and 47 per cent for the schoolgirls. The frequency distribution curves were not discriminated from each other: the two-sample rank test, known as the Mann-Whitney U-test (31, 51) gave an $x = \left(\frac{x-\mu}{\delta}\right)$ of 1.5 which was greater than 1.48, the critical value at $p = 0.07$ in the one-tail test, but less than 1.64, the corresponding value at $p = 0.05$. The distribution of the urinary glucose concentrations for the 4-year-old boys was practically identical with that for the girls.

It is apparent from Fig. 3 that only two girls had less than 2.0 mg of glucose per 100 ml of urine. One of these had a urinary glucose concentration of 1.8 mg per 100 ml or urine. This girl supplied two additional samples with 5.1 and 5.4 mg of glucose per 100 ml. None of her samples yielded any bacterial growth. Thus she may have not followed the instructions of restricted fluid intake. The other girl had 0.5 mg of glucose per 100 ml in the first-collected urine specimen and 0.4 mg per 100 ml in the second, but no growth on conventional culture. Culture for L-forms gave from both of these samples heavy growth of L forms that on subculture reverted to *E.coli*. In the following discussion this case is referred to the group with significant bacteriuria. Moreover, this case has been reported separa-

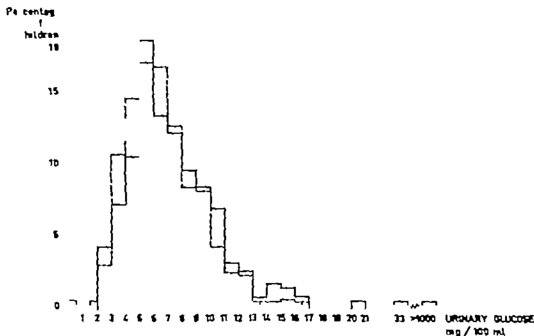


Fig 3 Percentage distribution of fasting urinary glucose concentrations in 338 schoolgirls 7 to 18 years old (—) and 564 4-year-old children of both sexes (—) supplying urine specimens yielding no bacterial growth on conventional culture.

tely (33). The borderline for subnormal urinary glucose was judged to be 2.0 mg per 100 ml, and thus at the same level as described earlier for adults.

It is demonstrated in Fig. 3 that 20 mg of glucose or more per 100 ml of urine was found in the samples from three subjects, all of whom were schoolgirls. One sample was collected from a schoolgirl with known diabetes. the glucose concentration was 1890 mg per 100 ml or urine. One girl with a family history of renal glucosuria brought a sample with 34 mg of glucose per 100 ml or urine the clinical examination at the Department of Pediatrics at the University Hospital of Lund confirmed the diagnosis of renal glucosuria The remaining girl had 20 6 mg of glucose per 100 ml of urine repeated samples from this girl showed less than 20 mg of glucose per 100 ml of urine This may indicate that the first sample was not collected in the fasting state even though the contrary was stated.

Bacteriological findings in relation to the urinary glucose concentrations

4-year-old children

The results of the bacteriological cultures of the urine specimens collected according to the instruction from the 788 children are given in Table II

Table II. Bacteriological findings in the first-collected urine specimens from 788 4-year-old children

Organism	Number of subjects with				Total
	N Growth	$<10^4$	10^4-10^5	$>10^5$	
N growth	564				564
E. coli		18	16	6	40
Coliforms		1	7	4	12
Enterococci		24	24		48
Staphylococci		3	7		10
Proteus mirabilis		13	13	2	28
Pseudomonas aeruginosa			3		3
Urinary nonpathogens		78	5		83
Total	564	137	75	12	788
Per cent	72	17	9.5	1.5	100

Coagulase-negative

Micrococci, diphtheroids, streptococci, as rule in mixed flora.

Viable count of "less than 10^4" or "10^4—10^5"

Out of the 212 children with growth of "less than 10^4" or "10^4 to 10^5" all had 2.0 mg of glucose or more per 100 ml of urine

E coli was observed in the urine from 34 subjects of whom 23 were girls (Table II) The second urine sample from these 34 subjects yielded growth of *E coli* in the specimens from six subjects. The urinary glucose concentrations were 2.0 mg or more per 100 ml in all six children. The viable count was "less than 10^4" in one and "10^4 to 10^5" in five From each of these six children, up to five additional urine samples were collected. Persistent growth of *E coli* was not demonstrated in any of these subjects All six children showed normal condition on clinical examination.

Coliforms were found in 8 subjects in none were the findings reproducible

Enterococci were present in the urine from 48 children, of whom 31 were boys. The findings of enterococci were reproduced in the second specimens from 10 subjects. From each of these up to four more urine specimens were collected no subject showed persistent growth of enterococci, and the urinary glucose concentrations were normal

The findings of coagulase-negative staphylococci in the urine from ten children were not reproduced on culture of additional specimens

The findings of *Pseudomonas aeruginosa* in the urine from three children were not reproduced on culture of additional specimens

Proteus mirabilis was found in the urine of 26 children, of whom 16 were boys. In the second urine samples the finding of *Proteus mirabilis* were repro-

duced in the urine from three girls and eight boys. All the specimens contained 2.0 mg of glucose or more per 100 ml. In additional samples from two of the three girls there was no bacterial growth. The third girl refused further investigation. From the eight boys another 30 urine specimens were collected. In the urine from four of them *Proteus mirabilis* was repeatedly found in each of four consecutive samples. The clinical examination of these four boys was normal pyelography was not performed. One of the four boys with reproducible findings of *Proteus mirabilis* supplied during a period of seven months three new samples with no growth. However nine months after the first specimen was collected, he fell ill with a high fever dysuria and pyuria. Two consecutive urine samples now yielded growth of *Proteus mirabilis* numbering more than 10^{5}" and "10^{3} to 10^{4} However the second sample with a viable count of 10^{3} to 10^{4}" was not collected as the first morning urine Intravenous pyelogram revealed a ureteral constriction and a dilated renal pelvis on the left side This patient is the only one out of 423 without significant bacteriuria at the time of screening in whom signs of disease was later found.

Altogether 267 second specimens were collected from the 4-year-old children who in the first urine specimens, had no growth, "less than 10^{3} or 10^{3} to 10^{4} All of these second samples each contained 2 0 mg of glucose or more per 100 ml of urine On culture of the second specimens more than 10^{5} was found in three subjects The organisms isolated were *Proteus mirabilis* coliforms and coagulase-negative staphylococci respectively In addition to the first two specimens collected from each of the three subjects, an additional eight samples were investigated. Significant bacteriuria was not confirmed in any of these subjects. Thus 1 1 per cent of the second specimens collected yielded a viable count of more than 10^{5}" but was not reproducible.

Viable count of more than 10^{5}"

More than 10^{5} organisms per ml of urine in the first-collected samples were found in 12 children (1 5 %) of whom seven had less than 1 0 mg of glucose one 1 4 mg of glucose and four had 2.0 mg of glucose or more per 100 ml of urine The bacteriological results were reproduced in six girls five of whom had less than 1 0 mg of glucose and one 1 4 mg of glucose per 100 ml of urine four had growth of *E coli* and two of coliforms Thus these six children had significant bacteriuria. In the girl with 1 4 mg of glucose per 100 ml of urine there was significant bacteriuria with growth of *E coli*. Her first sample was collected after an incubation time of 4 hours. A second and a third urine specimen collected from this subject with an incubation time of more than 6 hours, gave no measurable glucose i.e less than 0.2 mg per 100 ml This case illustrates the influence of the incubation time on the urinary glucose level in bacteriuria. The remaining six children with more than 10^{5} in which the bacteriological findings were not reproducible in further samples each supplied from one to eight new samples (Table

Table III. Viable counts on re-examination of six 4-year-old children with more than 10^5 organisms per ml of urine in the first-collected samples

Subject No.	Results of bacteriological analyses						No. of samples re-examined
	First-collected sample		Re-examination				
	Organism	Glucose mg/100 ml	No growth	$< 10^3$	$10^3 - 10^5$	$> 10^5$	
231	*E coli*						
	Enterococci	0.2	3	1	3	1	8
357	*Proteus mirabilis*						
	Enterococci	5 2	2	1	2		5
537	*P oteus mirabilis*						
	Enterococci	8 7	2				2
909	Coliforms						
	Pseudomonas aeruginosa						
	Enterococci	0 7	3				3
968	Coliforms	4 3	1				1
1020	*E coli*	5 2	1				1
Total number			12	2	5	1	20

III) The first samples collected showed a mixed flora in four subjects coliforms in one and *E coli* in one The urinary glucose levels were subnormal in two subjects (No 231 and No 909) and normal in the others. Cultures of new samples showed no growth in four of the subjects (Nos 537 909 968 and 1020) In the subject (No 231) with a urinary glucose concentration of 0 2 mg per 100 ml, the first culture yielded growth of E *coli* and enterococci. Eight more samples were obtained from this subject all of whom had a normal glucose content three displayed no growth, one "less than 10^3" three 10^3 to 10^5 and one yielded growth of more than 10^5 with the isolation of *Proteus mirabilis* The clinical examination of this case was normal One subject (No 357) showed in her first sample growth of *Proteus mirabilis* and enterococci. Five more samples showed either no growth or growth of varying organisms numbering either "less than 10^3" or 10^3 to 10^5 The clinical examination was normal.

Thus, in this material of 788 4-year old children 12 subjects showed in the first specimens collected a viable count of more than 10^5 The findings were reproducible in further samples from six of the subjects and thus they had significant bacteriuria The prevalence of significant bacteriuria in the 4-year-old girls was therefore 1 3 per cent In these six cases the diagnosis of bacteriuria was supported by the findings of subnormal levels of urinary glucose In the remaining six cases with more than 10^5 organisms per ml in a single sample but not reproducible the glucose values in two subjects were below normal (0 2 and 0 7

Table IV Bacteriological findings in the first-collected urine specimens from 505 schoolgirls

Organism	Number of subjects with				Total
	No Growth	$<10^3$	10^3-10^4	$>10^4$	N
No growth	339				339
E coli		9	12	5	26
Coliforms		1	2	2	5
Proteus mirabilis		1	1	1	3
Enterococci		4	6	1	11
Staphylococci[a]		6	7		13
Pseudomonas aeruginosa				1	1
Urinary nonpathogens[b]		103	5		108
Total N	339	124	33	10	505
Per cent	67	25	6	2 ✓	100

Including one subject with heavy growth of L-forms of *E. coli*.
Coagulase-negative
Micrococci, diphtheroids, streptococci, as rule in a mixed flora

mg per 100 ml) whereas in the remaining four they were above 2.0 mg per 100 ml of urine

Schoolgirls

The results of the ordinary bacteriological cultures of the first urine specimens collected according to the instructions from 505 schoolgirls are presented in Table IV

Viable count of less than 10^3 or 10^3 to 10^4"

Less than 10^3 or 10^3 to 10^4 were found in 157 schoolgirls (31 %) Table IV All of them had 2.0 mg of glucose or more per 100 ml of urine

E coli was present in 21 subjects New samples showed still normal urinary glucose values. Three samples had growth of *E coli* also in the second specimen, *10^3 to 10^4" in one* and "less than 10^3 in two From each of these three subjects four additional samples were collected. From one of these girls the samples persistently yielded growth of *E. coli* but in an amount of "less than 10^3 None of the three girls had clinical signs or anamnestic data of urinary tract infections. Thus although *E coli* was persistently found in one case the fact that the clinical examination and the anamnestic data revealed normal conditions may support the assumption that the repeated findings of low grade growth of *E coli* was probably due to contamination.

Coliforms were observed in the urine from three subjects and *Proteus mirabilis*, in two subjects Persistent growth of the same organisms was not found in cultures from additional samples from these five subjects

Enterococci were seen in the urine of 10 subjects six of whom had 10^3 to 10^4. Enterococci were demonstrated also in the second sample from two of these 10 girls but in none were enterococci observed in further samples

The findings of coagulase-negative staphylococci in the urine of 13 school girls was not reproducible in new samples

Growth of urinary nonpathogens was found in the samples from 108 schoolgirls. More than 10^5 organisms per ml were not found in additional samples

In the material of schoolgirls second specimens were collected from 93 children with either no growth and a previous history of urinary tract infection or with growth of "less than 10^3 or 10^3 to 10^4. All these second specimens showed 2.0 mg of glucose or more per 100 ml of urine The second specimen from one girl showed more than 10^5 Her first urine specimen manifested no bacterial growth and the second a mixed flora with growth of *E coli* *Pseudomonas aeruginosa* and diphtheroids. Two further samples from this girl yielded no bacterial growth.

Viable count of more than 10^{5}"

More than 10^5 organism per ml of urine in the first-collected samples were found in 10 schoolgirls or 2 per cent (Table IV). The urinary glucose concentrations were below 1 0 mg in 7 and above 2 0 mg per 100 ml of urine in three subjects New samples showed in the seven subjects with subnormal levels of urinary glucose identical bacteriological results—significant bacteriuria.

The remaining three subjects with normal urinary glucose levels and more than 10^{5}" had in the first samples growth of *Proteus mirabilis* coliforms and *Pseudomonas aeruginosa* respectively whereas their second samples showed no growth. Thus they did not have significant bacteriuria. The prevalence of significant bacteriuria was therefore 1 6 per cent in schoolgirls if the case with bacterial L forms is included

Summary of findings in the 4-year-old children and the schoolgirls

Table V shows that a total of 17 children had less than 2.0 mg of glucose per 100 ml of urine Out of these 14 had significant bacteriuria two had more than 10^4 in a single sample and one had no growth. Among the 1 276 children with urinary glucose concentrations of 2.0 mg more per 100 ml none had significant bacteriuria.

The test paper gave no color reaction for the 16 specimens containing less than 1 5 mg of glucose per 100 ml of urine and for two of the 1 276 samples containing 2.0 mg or more per 100 ml.

Population study

The results of the bacteriological cultures of the first urine specimens collected from the 2,391 females that had followed the instructions are presented in Table VI

No growth "less than 10^3 or 10^3 to 10^4"

"No growth was found in the urine specimens from 1,367 subjects (57 %)

Tabl V. Comparison of the glucose concentrations with viable counts in 1,293 4-year-old children and schoolgirls

Urinary glucose mg/100 ml	Bacteriological findings				T tal
	No growth	$< 10^4$ or $10^4 - 10^5$	$> 10^5$ Not reproducible	$> 10^5$ Reproducible[1]	
< 1.0			2	13[2]	15
1.0 – 1.4				1	1
1.5 – 1.9	1				1
≥ 2.0	900	369	7		1276
Total	901	369	9	14	1293

[1] Significant bacteriuria.
Including one subject with L-forms f *E. coli*.

Table VI. Bacteriological findings in the first-collected urine specimens from 2,391 females in the population study

Organism	Number of ubjects with						Total
	N growth	$< 10^4$	$10^4 - 10^5$	$> 10^5 - 10^6$	$> 10^6 - 10^7$	$> 10^7$	
No growth	1,367						1,367
E. coli		29	50	20	35	35	169
Coliforms		8	16	4	6	6	40
Proteus mirabilis		6	6				12
Enterococci		35	38	5		1	79
Pseudomonas aeruginosa							0
Staphylococci		1	53	9		1	66
Urinary nonpathogens		363	207	63	23	2	658
Total	1,367	442	370	101	66	45	2,391
Per cent	57	19	15	4	3	2	100

Coagulase-negative
Micrococci, diphtheroids streptococci as rule in a mixed flora.

The test paper gave a normal color reaction in 1,340 (98 %) a faint color reaction in 18 and no color reaction in nine subjects "Less than 10^4 or 10^4 to 10^5 were present in the specimens from 812 subjects. The test paper gave a normal color reaction in 786 (97 %), a faint color reaction in 22, and no color reaction in four specimens.

Normal color reaction

Among the 786 subjects supplying specimens giving a normal color reaction, 362 had 10^5 to 10^{8*} (Table VII) Among the 362, second samples were obtained from 127 subjects of whom 82 in their first samples had growth of *E coli* coliforms *Proteus mirabilis* or enterococci, and 45 had growth of coagulase-negative staphylococci or urinary nonpathogens

In 21 of the 127 subjects the results from the first specimens were reproduced. 10 had growth of *E coli*, three of coliforms three of *Proteus mirabilis* and five of enterococci. Each of these 21 subjects supplied at least a further four samples only the samples from one of them showed persistent growth of the same organism. This subject had 10^5 to 10^{8*} *E coli* in the two first-collected samples and a normal color reaction, whereas the following sample showed more than 10^{8*} *E coli* and no color reaction with the test paper Thus, this subject developed significant bacteriuria, which was also disclosed by the test paper An intravenous pyelogram in this subject showed normal conditions. Intravenous pyelograms were made on 18 more of the 21 subjects 15 were normal, two had a duplex pelvis; and one a dilated ureter The three subjects with positive X-ray findings had a maximal concentration capacity exceeding 700 mOsm per kg and an excretion rate of WBCs below 400 000 per hour One of the subjects with a duplex pelvis had a past history of urinary tract infections.

Among the remaining 106 urinary pathogens were persistently found only in one subject. In this subject with *E coli* in the first sample an additional four samples collected during a period of five months, showed persistently growth of coliforms with a viable count of more than 10^5 The test paper gave no color reaction in these four samples and the urinary glucose concentrations were below 1 0 mg per 100 ml in all of them. The pyelogram showed papillary necroses in the right kidney the concentration capacity was less than 700 mOsm per kg and the excretion rate of WBCs exceeded 400 000 per hour She was found to have a past history of urinary tract infections Thus, this case probably had bacteriuria even at the time of screening; she escaped detection both by the bacteriological culture and by the test paper in the first-collected specimen but was later disclosed by both methods.

Tabl VII. Organisms found in 786 urine samples with viable counts of *less than 10^5 or *10^5 to 10^8 organisms per ml of urine and giving normal color reaction with Uriglox®

Organism	Viable counts		Total
	$<10^5$	10^5-10^8	
E. coli	27	50	77
Coliforms	7	16	23
Proteus mirabilis	6	6	12
Enterococci	33	37	70
Staphylococci[1]	1	51	52
Urinary nonpathogens	350	202	552
Total	424	362	786

Coagulase-negative

Micrococci, diphtheroids streptococci, as rule in a mixed flora.

Table VIII Viable counts and urinary glucose concentrations in 42 urine specimens giving faint color reaction with Uriglox®

Urinary glucose mg/100 ml	Number of subjects with				Total
	No growth	$<10^4$	10^4-10^5	$>10^5$	
<1.0					0
1.0–1.4	1	1	1		3
1.5–1.9	3	3		1	7
2.0–2.9	10	6	4	1	21
≥3.0	4	6	1		11
Total	18	16	6		42

Faint color reaction

A faint color reaction was obtained from 18 specimens with no growth and from 22 specimens out of the 812 with a viable count of "less than 10^3" or 10^4 to 10^5 (Table VIII). The urinary glucose concentrations were subnormal in nine subjects; 1.0 to 1.4 mg in three and 1.5 to 1.9 mg in six subjects. The concentrations of creatinine in the urine in the specimens with subnormal urinary glucose varied between 25 and 50 mg per 100 ml and the osmolalities varied between 100 and 275 mOsm per kg, indicating that the low glucose values probably were caused by an elevated diuresis. New samples were collected from 14 subjects nine of whom in their first samples had 1.0 to 1.9 mg of glucose per 100 ml of urine and five of whom had 2.0 mg or more per 100 ml of urine and a viable count of 10^3 to 10^4. The second samples gave for all but one normal color reactions and no growth and the urinary glucose concentrations were 2.0 mg or more per 100 ml. In the samples in which the urinary glucose concentrations exceeded 2.0 mg per 100 ml the creatinine concentrations exceeded 100 mg per 100 ml and the osmolalities 500 mOsm per kg. The single subject who still had abnormal findings showed 1.3 mg of glucose per 100 ml of urine both in the first sample and in the second one. The bacteriological culture displayed no growth in the second sample. Culture for L-forms and slow-growing organisms were negative in both the first and the second samples. The concentration of creatinine in the urine was about 50 mg per 100 ml, and the osmolality about 350 mOsm in both samples. The subject refused further investigation.

No color reaction

No color reaction was obtained from 13 specimens with no growth or low grade growth (Table IX), nine revealed no growth, and four revealed growth of coagulase-negative staphylococci and urinary nonpathogens, respectively. The concentrations of creatinine in the urine and the osmolalities were low less than

Table IX. Viable counts and urinary glucose concentrations in 98 urine specimens giving no color reaction with Uriglox®

Urinary glucose mg/100 ml	Number of subjects with						Total
	No growth	$< 10^3$	$10^3 - 10^4$	$> 10^4 - 10^5$	$> 10^5 - 10^6$	$> 10^6$	
< 1.0				11	27	37	75
1.0 – 1.4			1	1	4	2	8
1.5 – 1.9	5	1	1		2	1	10
2.0 – 2.9	1	1					2
≥ 3.0	3						3
Total	9	2	2	12	33	40	98

50 mg per 100 ml and less than 375 mOsm per kg in all the eight specimens with subnormal urinary glucose. New samples showed in all the 13 subjects no growth, and urinary glucose values of 2.0 mg or more per 100 ml in all samples but one. At least seven of the eight subjects supplying samples giving subnormal urinary glucose initially probably had not followed the instructions of restricted fluid intake since the concentrations of creatinine in urine as well as the osmolalities were low in the first specimens but not in the repeated samples collected. In the remaining subject with reproducible findings of subnormal urinary glucose in the second and an additional three samples, all the four consecutive samples showed no growth. In this subject an intravenous pyelogram showed an atrophic left kidney measuring 8 × 3 cm, enlargement of the right kidney with hydronephrosis and papillary necroses. No L-forms or slow-growing organisms could be demonstrated. She had isosthenuria which presumably caused the low urinary glucose concentration.

More than 10^5

Viable counts exceeding 100 000 organisms per ml of urine were present in the first specimens from 212 (8.9 %) of the 2,391 females (Table VI). The test paper gave no color reaction for 85, a faint color reaction for two and a normal color reaction for 125 of these 212 specimens (Table X).

No color reaction

Of the 85 specimens with viable counts of more than 10^{5} and giving no color reaction 79 were supplied by subjects who subsequently were shown to have significant bacteriuria. *E. coli* was present in 67, coliforms in 11 and achromobacter in one subject (Table X). The urinary glucose concentrations were below 1.0 mg per 100 ml in 61 of the 67 subjects with *E. coli*, in four it was 1.0 to 1.4 mg, and in two 1.5 to 1.9 mg per 100 ml. In all 11 subjects with growth

Table X. Bacteriological findings and color reaction of Uriglox® in 212 urine specimens with viable counts of more than 10^5 organisms per ml of urine

Organism	Not significant bacteriuria			Significant bacteriuria		Total
	Normal color	Faint color	No color	Normal color	No color	
E. coli	14		3	6	67	90
Coliforms	3		2		11	16
Enterococci	6					6
Staphylococci[1]	12					12
Urinary nonpathogens[2]	84	2	1		1	88
Total	119	2	6	6	79	212

[1] Coagulase-negative.
[2] Micrococci, diphtheroids, streptococci, as a rule in a mixed flora

of coliforms and in the subject with achromobacter the urinary glucose concentrations were below 1.0 mg per 100 ml.

The diagnoses of bacteriuria were based on two consecutive cultures in 31 subjects and in 48 subjects on 3 to 11 consecutive cultures made during a period of two to seven months. Thus in 37 subjects four or more consecutive samples gave growth of the same organisms with viable counts exceeding 100 000 organisms per ml associated with subnormal levels of urinary glucose and no color reaction with the test paper. The results indicate that the glucose method uncovered subjects with bacteriuria that was persistent. The concentrations of creatinine in the urine and the osmolalities of those samples collected for comparison of the viable counts with the glucose concentrations from the 79 subjects with significant bacteriuria varied between 90 and 200 mg per 100 ml, and 400 and 1 000 mOsm per kg, respectively in all but three subjects. These three subjects showed creatinine values around 50 mg per 100 ml of urine and osmolalities around 250 mOsm per kg; their maximal concentration capacities were 510 to 590 mOsm per kg.

The subject with growth of more than 10^5 achromobacter a microorganism generally considered as nonpathogenic to the urinary tract was found to have an atrophic left kidney measuring 7.5×3 cm, with several small parenchymal calcifications. The right kidney was normal. She had no actual complaints or past history of urinary tract infections. After treatment with antibiotics she had urinary glucose values of 2.0 mg or more per 100 ml and no growth in seven samples collected over a period of five months.

All but five of the 79 subjects with significant bacteriuria and subnormal

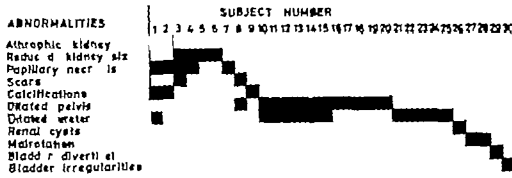


Fig. 4 Abnormal findings in the intravenous pyelograms of 30 cases with significant bacteriuria.

levels of urinary glucose were clinically examined, four subjects preferred to consult their own physicians and one refused further investigation. two of them had pyelonephritis, which had been previously diagnosed, one had diabetes with nephropathy and one had an ureterocolostomy

Intravenous pyelography was made in 67 of the 79 subjects with significant bacteriuria. Positive findings were reg-recorded in 30 (45 %) of the 67 subjects (Fig 4) The excretion rate of WBCs exceeded 400,000 per hour in 71 per cent and the maximal capacity to concentrate the urine was less than 700 mOsm in 31 per cent of the 74 subjects; a positive past history of urinary tract infections was present in 38 per cent, and 30 per cent had actual complaints suggestive of urinary tract infection, but it had in none led to consultation with physicians Only seven of the 74 subjects were normal in all respects regarding X-ray concentration capac ity excretion rate of white blood cells, past history or actual complaints of urinary tract infections

The remaining six subjects out of the 85 with no color reaction and more than 10^{5} in the first-collected samples, did not have reproducible findings of more than 10^{5} The urinary glucose concentrations were below 1 0 mg per 100 ml in four subjects: two had growth of *E coli* one of coliforms, and one of urinary nonpathogens. In two subjects the concentrations were 1 1 mg and 1.2 mg of glucose per 100 ml of urine one had growth of *E. coli* and one of coliforms. All urine specimens had creatinine concentrations and osmolalities indicating that the low glucose values were not due to elevated diureses. Five of the six samples were adequately chilled whereas the sample showing growth of uri nary nonpathogens had not been chilled. Three subjects had no history of urinary tract infections; their pyelograms were normal and each subject supplied four additional samples revealing no growth or low-grade growth of urinary nonpathogens. The remaining two subjects had actual complaints of cystourethritis at the time when their first samples were collected. Clinical examinations includ

ing pyelograms were made three weeks after screening and were normal in both subjects. Each of them supplied two additional samples revealing "no growth" and normal urinary glucose concentrations.

Faint color reaction

A faint color reaction on the test paper was observed in two of the 212 samples revealing "more than 10^5" (Table X). In both samples there was growth of urinary nonpathogens. The urinary glucose concentrations were 1.8 mg and 2.2 mg per 100 ml, respectively. The creatinine concentrations and the osmolalities were low in both of these samples. New samples showed in each subject normal chemical results and "no growth."

Normal color reaction

Of the 125 subjects supplying specimens with "more than 10^5" and giving normal color reaction for the test paper, 20 showed growth of *E. coli*, three of coliforms, six of enterococci, 12 of coagulase-negative staphylococci, and 84 of urinary nonpathogens (Table X). Second samples were obtained from the 41 subjects with growth of urinary pathogens and from 20 of the 84 subjects with growth of urinary nonpathogens.

*Reproducible findings with growth of the same organisms at levels of "more than 10^5"—significant bacteriuria—*were found in six of the subjects with *E. coli*. Their second samples still showed color reactions for the test paper and glucose values of 2.0 mg or more per 100 ml. In one of them the "bacteriuria" disappeared when a tampong was adapted into the vagina prior to the collection of additional specimens. One of them had actual symptoms of uretritis at the time of screening and showed "more than 10^5" *E. coli* in three consecutive samples, all with normal color reactions. In an additional six consecutive samples, collected from this subject over a period of three months, there was "no growth" and she had no symptoms—the pyelogram and her maximal concentration capacity were normal. *Of the remaining four subjects with reproducible findings of "more than 10^5"* one brought 11 samples over a period of seven months: all showed normal urinary glucose and "more than 10^5" *E. coli*; three subjects each returned three samples with "more than 10^5" *E. coli* and after treatment with antibiotics several samples with "no growth." The intravenous pyelograms were normal in three of these four subjects and showed a dilated ureter in one; the concentration capacities were normal in all four subjects.

Among the remaining 35 out of the 41 subjects with growth of "more than 10^5" urinary pathogens in the first collected sample, eight had growth of the same organism in the second sample, but in an amount of "less than 10^3" *or* "10^3 to 10^5." *E. coli* was found in six and coagulase-negative staphylococci in two subjects. Only one of these subjects showed subsequently growth of the same organism, *E. coli*. This subject brought nine samples with viable counts varying between "less than 10^3" and "more than 10^5," either with growth of *E. coli* alone or in a mixed flora. She had no actual complaints or past history of urinary tract infections; the pyelogram was normal, and her

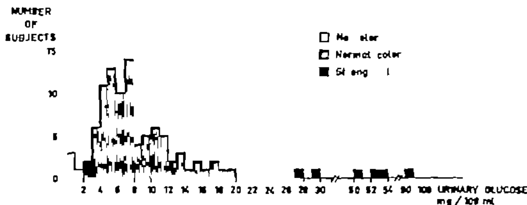


Fig 5 Fasting urinary glucose concentrations and the color reaction of Uriglox® in 101 pregnant women.

maximal concentration capacity was 1 210 mOsm per kg. All of her samples gave a normal color reaction and the urinary glucose concentrations were 2.0 mg or more per 100 ml. The other five subjects with *E coli* in their second sample showed no growth subsequently The pyelograms were normal in three and disclosed dilated ureters in two their maximal concentration capacities were normal The two subjects with staphylococci in their first two collected samples showed normal findings on further follow-up studies

Among the 20 subjects with more than 10^5 urinary nonpathogens none had reproducible findings in repeated samples

Pregnant women

Among the 67 subjects with significant bacteriuria with growth of *E coli* four were pregnant· three had less than 1 0 mg, and one had 1 8 mg of glucose per 100 ml of urine the test paper gave no color reaction. In the total population study 115 were pregnant and thus significant bacteriuria appeared in 3.5 per cent of the pregnant women. The pregnant women were controlled with new samples once a month during pregnancy No significant bacteriuria developed among those who had no growth or low-grade growth of bacteria in their first-collected samples. Growth of urinary nonpathogens in amounts exceeding 100 000 organisms per ml were common, but it was in no case correlated to subnormal levels of urinary glucose. The urinary glucose concentrations were determined for 101 pregnant women. These results are illustrated in Fig. 5

Evaluation of the test paper in screening for significant bacteriuria

For evaluation of the test paper in screening for significant bacteriuria, the total material of 1 459 4-year-old chil-

dren and schoolgirls, and the 2,452 females in the population study a total of 3,911 subjects were considered irrespectively if they had followed the instructions or not. No color reaction on the test paper was considered as an indication of bacteriuria and a color reaction even if faint as normal. Out of the 3,911 subjects 97 were judged to have bacteriuria and of these the test paper disclosed 93 (96 %). Two of these 97 subjects one case with L forms of *E. coli* and one case with growth of achromobacter would not have been detected if the bacteriological method alone had been used for screening. Among the 3 814 subjects without significant bacteriuria, the test paper gave color reactions for 3 784 (99.2 %) and thus a false indication of bacteriuria in less than 1 per cent.

Discussion

The prerequisite for a meaningful discussion on bacteriuria in population studies is that the concept of true bacteriuria, and of significant bacteriuria are understood and that a finding of more than 10^5 organisms per ml in a single sample is evaluated in relation to the frequency of contamination. A possibility to distinguish between contamination and bacteriuria based on quantitation of the organisms has been calculated from analyses of the distribution of colony counts in patients with and without clinical evidence of active infection of the urinary tract (20-23). The most important finding indicating a biological difference between "low count and "high-count patients was the results of the analyses of the second specimen, obtained approximately one week later from each patient. Repeated cultures of clean-voided specimens from the same patient led to the finding that many of those with more than 10^5 on the first count subsequently had lower counts. Contrary to this, the typical finding in bacteriuria—was that the findings of significant levels of more than 10^5 were reproducible. And so significant bacteriuria was defined by Kass, as the findings of more than 10^5 in two consecutive samples. However the confidence level of this concept in reflecting true bacteriuria is dependent on the type of clinical material under study the technique used for sampling the urine and the handling of the urine specimen after sampling. The level of confidence should therefore be worked out for each study on the basis of the percentage of successive cultures giving more than 10^5 colonies per ml of urine (Cohen and Kass 1968 (5)). It has been found that whatever the means used to obtain clean-voided urine specimens contamination is almost unavoidable in a proportion of the population studied. According to Norden and Kass (35) the frequency of specimens contaminated at a level of more than 10^5 should not exceed 4 per cent of the total number if adequately sampled and then the confidence level of two consecutive samples from each patient in a general female population will be above 95 per cent to predict reproducible findings. This means that a maximum of five out of 100 subjects with significant bacteriuria can be suspected to contaminate repeatedly and thus not represent cases of true bacteriuria. To date the only truly reliable method to differentiate this type of contaminator from bacteriurics is culture of urine obtained by percutaneous bladder puncture unavailable to most physicians.

An assessment of present chemical methods for detection of bacteriuria is complicated by the lack of suitable confidence data for the reference methods and also by the lack of the establishment of definitive criteria for use in the diagnosis of bacteriuria.

The Griess nitrite test has received the most attention and has been studied in more than 40 000 individuals (1 9 10 15 17 24 25 37 38 46-48 50 52) However studies adequately defined to permit a comparison with the present study are few Finnerty et al. (15) compared the data of the modified Griess nitrite test (Stat test) performed on first-morning voided specimens and colony counts performed on cleanly caught mid-stream specimens from 624 asymptomatic pregnant women. Bacteriuria was defined as a colony count greater than 80 000 bacteria per ml of urine on three separate days Serial colony counts eliminated 15 specimens that were labelled positive after the first culture In the 30 subjects labelled as bacteriurics the nitrite test gave a false negative result in seven—thus giving the method a sensitivity of 77 per cent. The falsely positive results were 11 or 2 per cent. Further studies showed that 18 (2.9 %) were nitrate-nitrite negative and among them all seven of the missed cases occurred. Thysell (48) found that in 18 6 per cent of the tested urine the supply of nitrate was insufficient In a series of 1 665 apparently healthy women, 40 to 62 years old Wallmark et al. (50) used the same criteria for the diagnosis of bacteriuria as in the present study and collected the urine samples after at least 5 hours of incubation in the bladder They found a sensitivity of 84 per cent for the nitrite test whereas the specificity was almost 100 per cent. In an extensive study (1) covering approximately 20 000 prenatal patients by the Chicago Board of Health, 57 528 urine specimens were obtained for screening for significant bacteriuria by the nitrite test. However only in a part of the study the criteria for diagnosis were strictly defined and in this part 21 per cent of the urine samples were found to be falsely nitrite-test negative for significant bacteriuria as confirmed by culture of catheterized specimens.

Bullen and Kincaid Smith (3) summarize the reasons for the failure with the nitrite-test as a lack of sufficient nitrate in the urine a lack of time for the enzyme nitrate reductase to be produced by the bacteria owing to urinary frequency an insufficient concentration of nitrite due to diuresis acidification of urine a further reduction of the nitrite due to retention of urine very high bacterial counts, and infection by a bacteria that produces little or no nitrate reductase

The catalase test (Braude and Berkowitz 1961 (2)) has clear shortcomings in that common urinary pathogens as enterococci, *Klebsiella-Aerobacter* and some strains of *E coli* lack or contain less catalase than other urinary pathogens, further catalase from erythrocytes or epithelial cells render the method a low specificity (24 28 32, 48)

The triphenyl tetrazolium chloride test introduced by Wundt (53) and

developed by Simmons and Williams (45) for screening purposes has been extensively employed for screening of bacteriuria. Only in few instances the high sensitivity of 94 per cent obtained by Simmons and Williams has been reached (4 11 24) Kincaid Smith et al. (24) detected 86 to 89 per cent of the bacteriurics in 3 000 pregnant women and found only 2 per cent false positive tests, whereas Eliot and Pryles (12) observed 30 per cent false negative tests Neter (34) adds still more contradictory results with 33.3 to 43 7 per cent false negative and 2.2 to 10 4 false positive tests However in these studies the diagnostic criteria of significant bacteruria are not strictly defined nor are the confidence levels of the reference methods In a well defined study (Constable 1966 (6)) the TTC test detected 86 6 per cent of the subjects with reproducible findings of more than 10^5 and the false positive tests were 2.7 per cent.

The main defect of the TTC test is that the formation of adenosine triphosphate by the bacterial cells is reduced in the presence of TTC which is therefore toxic to the bacteria and will inhibit the chemical reaction (3); furthermore staphylococci and some forms of *Proteus* and *Pseudomonas* will not reduce TTC The high rate of false positive results may be referred to the need for 4 hours of incubation at 37° C of urine in vitro in the presence of the TTC reagent and in some cases to the presence of ascorbic acid in the urine specimen (18 48 54)

In the present study cultures of the first-collected urine specimens showed more than 10^{5}" in 246 samples: gram negative rods were found in 133 enterococci in seven, staphylococci, in 14 and urinary nonpathogens in 92 samples. Second samples showed reproducible findings in 98 instances which indicated that at least 3 8 per cent of the population (148 out of 3,911) had been contaminated at a level of more than 10^5 considering only gram-negative rods this frequency was 0.9 per cent. Serial counts eliminated two more individuals, one in whom the source of contamination was the vagina, and one who had acute symptoms of urethritis at the time of screening Thus two consecutive cultures with more than 10^{5}" and growth of the same organisms predicted persistent bacteriuria at a confidence level of 98 per cent One case showed reproducible growth of L forms of *E coli* and therefore 97 subjects were judged to have true bacteriuria

"The glucose method, as employed quantitatively and semiquantitatively correctly diagnosed 93 (96 %) of the 97 subjects with true bacteriuria. The explanation for the subnormal urinary glucose in these cases is supposed to be that the microorganisms had consumed the urinary glucose within the urinary tract above the urethra. Increased diuresis was eliminated as the cause of the low glucose values in these cases In a therapy trial (to be published) all those receiving no treatment over a period of up to seven months showed in consecutive samples persistently growth of more than 10^{5}" and a permanently subnormal urinary glucose whereas in those given adequate therapy the urinary glucose normalized. In case of

relapse subnormal levels of urinary glucose were again found.

The glucose method gave false negative results in four (4 %) of the 97 subjects with bacteriuria. In three of them the bacteriuria disappeared after treatment and the urinary glucose remained at the same normal level as observed before treatment was initiated. The possibility of contamination cannot be excluded in these cases since bladder puncture was not performed.

A false indication of bacteriuria by the glucose method was obtained in 30 (0.8 %) out of the total (3,814) subjects and thus, the reliability of the method to disclose nonbacteriurics was above 99 per cent. Hydration, with an increased diuresis and therefore a dilution effect on the urinary glucose was the probable cause in most of the subjects with a false positive test. Renschler et al. (36) found urinary glucose values below 2.0 mg per 100 ml when the diuresis exceeded 1.5 ml per minute. Among the nine subjects with more than 10^5" and subnormal urinary glucose in the first samples but not reproducible, hydration was excluded as the cause of the low glucose in six subjects: two had symptoms suggestive of acute cystourethritis at the time when their first samples were collected whereas four were asymptomatic. It cannot however be excluded that some of the subjects with a nonreproducible finding of more than 10^5 actually had bacteriuria in the sense that bacteria were present in the urine within the host at the time of screening in spite of the fact that significant bacteriuria was not confirmed. However if this was the case the bacteria had not yet established themselves persistently above the urethra.

In a few cases the test paper gave no color reaction even though the samples contained a normal urinary glucose concentration. The explanation of these false reactions may be incorrect handling of the test papers, diminished ion exchange capacity in the test paper or an extremely high concentration of ascorbic acid in the urine which acts as an inhibitor for the glucose-oxidase reaction.

In the present study special attention was paid to subjects with a low-grade growth of urinary pathogens ("less than 10^3 or "10^3 to 10^5"). Kass (21) found from studies of hospitalized patients that about 0.5 per cent of bacteriurics can be expected, at any time to have colony counts below 10^5. Our results indicate that in population studies provided the first morning urine is used for culture the number of bacteriurics with accidentally lower counts is still lower. Only in two out of 1 181 subjects with low grade growth at the time of screening, significant bacteriuria was confirmed in the nearest weeks after screening, and then, also the glucose method indicated bacteriuria. A third subject, a 4-year-old boy with reproducible findings of low grade growth of *Proteus mirabilis* and normal urinary glucose developed signs of urinary tract disease 9 months after screening.

Thus, the results give strong support for the validity of the quantitative approach (20, 21) for detection of infection within the urinary tract.

The glucose method requires that the

urine be obtained from a fasting individual and would of course be invalid in the presence of higher levels of glucosuria. It also requires a retention time of urine in the bladder long enough to permit the bacteria to reduce the urinary glucose to subnormal levels How limiting, in practice these requirements were was studied. In only one girl, who had a meal half an hour before the collection of the urine specimen the glucose concentration, 30 mg per 100 ml, exceeded the normal range In the population study the glucose concentrations were determined quantitatively for ten samples depending on an intensive color reaction on the test paper Eight of these samples had a glucose concentration varying from 30 to 6 800 mg per 100 ml and led to the detection of earlier unknown diabetics Two other samples containing 41 and 240 mg per 100 ml were shown not to have been collected in the fasting state

Among the 115 pregnant women within the population study quantitation of urinary glucose was performed in 101 subjects The frequencies of fasting urinary glucose concentrations in the range of 15 to 20 20 to 50 and 50 to 100 mg per 100 ml were 7 4 and 4 per cent respectively Our material of pregnant women is still too small to permit a statistical comparison of fasting urinary glucose concentrations during pregnancy with that of nonpregnant adult women found earlier (40). However pregnant women in the fasting state seem to have a higher frequency of hyperglucosuria than nonpregnant women. Fine (13 14) found more than 15 mg of glucose per 100 ml of urine in 25 per cent during pregnancy as compared with the 3 7 per cent in nonpregnant women these results were however not obtained from urine of fasting women. Fine (14) concluded that in pregnancy there is a significant increase not only in urine with raised glucose content but also in urine with low glucose content (less than 1 0 mg per 100 ml)- 4.9 per cent of the 1 000 urine specimens contained 0 to 1 mg of glucose per 100 ml. He ascribed the hypoglucosuria to an enhancement of tubular reabsorption due perhaps to a reduction in corticosteroid action, and assumed that an increased output of insulin was responsible for this reduction. The possibility of bacteriuria causing the low glucose values was not discussed.

In vitro studies have shown (43) that urinary glucose concentrations up to 100 mg per 100 ml may be reduced to less than 2 0 mg per 100 ml after 6 hours of incubation at 37° C This indicates that the glucose method may be suitable for detection of bacteriuria also in cases where the renal excretion of glucose is at the upper limit of the normal range. This has, however not been proved in the present study The value of the glucose method for screening purposes in pregnancy can not be finally established as the series of pregnant women yet are small.

A retention time of six hours or more was easily obtained in this study of apparently healthy subjects after instruction by letter only There was no evidence that asymptomatic significant bacteriuria was accompanied by more frequent voiding than was recorded in subjects without bacteriuria. The

advantage of collecting the urine specimens at home was not appreciably reduced by incorrect handling of the urine samples. The frequency of specimens showing no growth 62 per cent was of the same magnitude as that obtained by Lemieux (26), who found 69 per cent after thorough perituretheral washing performed at a hospital. In the present study periuretheral cleansing was recommended only in the population study and then with dry swabs only since according to our experience heavy dampened swabs involve a risk of severe contamination from the perineum. Turner (49) found that vulvar cleansing performed by the person to be examined did not significantly reduce the frequency of contamination, and in a recent investigation by Linton and Gillespie (30) it was found that whether the vulva was swabbed with saline or not had no influence on the frequency of contamination.

The value of bacteriological cultures for detection of true bacteriuria is limited by the techniques employed for collecting and handling the samples. When applying the glucose method for detection of bacteriuria, there is no need for clean-voided specimens and the urine can be transported to the laboratory without other treatment than adding a preserving disinfectant. However the quantitative determination of urinary glucose requires a laboratory with trained personnel which in screening for bacteriuria is impractical. Our results demonstrate that the test paper is a simple quick, and reliable way to discriminate those in a general population to which bacteriological studies would still be needed. The test paper gave no color reaction and thus indicated bacteriuria in all those cases that the quantitative glucose method disclosed as bacteriurics. With reference to the bacteriological method, the test paper disclosed 96 per cent of the subjects with true bacteriuria whereas the false indications of bacteriuria were less than 1 per cent. In comparison, a finding of more than 10^5 organisms per ml of urine in the first-collected specimens yielded false indications of bacteriuria in 4 per cent (150 out of 3 814) and if gram-negative rods only were considered, false positive results were obtained in 1 per cent (38 out of 3 814) The confidence level of a single specimen with growth of more than 100 000 organisms per ml to predict significant bacteriuria was only 39 per cent (96 out of 246). The confidence level of a single specimen with subnormal urinary glucose to predict significant bacteriuria was 76 per cent (93 out of 123) Furthermore the test paper picked up two cases that would have been missed if routine cultures had been employed alone

Concluding remarks

The borderline of normal and subnormal levels of urinary glucose is 2.0 mg per 100 ml in adults and children.

Provided a retention time of urine in the bladder of at least 4 to 6 hours, urinary glucose levels below 1.0 mg per 100 ml are regularly associated with significant bacteriuria indicating bacterial multiplication within the urinary tract above the urethra.

Urinary glucose levels between 1.0 and 2.0 mg per 100 ml may occur in bacteriurics and also in nonbacteriurics if the fluid intake during the night is not restricted.

Provided urine samples are obtained in the fasting state after a retention time of at least 4 to 6 hours urinary glucose levels above 2.0 mg per 100 ml indicate in a general population, absence of bacteriuria.

The semiquantitative test-paper method (Uriglox®) for differentiating between subnormal and normal levels of urinary glucose was shown to give results that were in agreement with those of the quantitative glucose method.

The glucose method seems to be a valuable complement to the bacteriological technique in differentiating between contamination and bacteriuria and offers a simple means for mass detection of bacteriuria.

The sensitivity of the glucose method was 96 per cent and its specificity above 99 per cent. The confidence level of a single specimen with subnormal urinary glucose in predicting significant bacteriuria was almost twice as high as that of a single specimen with more than 100 000 organisms per ml.

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Supplementum 505

Single-blind Randomised Multicentre Trial Comparing Heparin and Streptokinase Treatment in Recent Myocardial Infarction

By A. Amery G Roeber H J Vermeulen and M. Verstraete

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o leuven-belgium

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Single blind Randomised Multicentre Trial Comparing Heparin and Streptokinase Treatment in Recent Myocardial Infarction

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Leuven 1969

We are grateful to the investigators of different European Centres who collaborated in this joint programme

– Stadtische Krankenhaus-Schwabing Munchen Germany	Prof H Begemann Priv Doz. Dr E König Dr G Roeber
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INTRODUCTION

When this study was commenced in 1962 the results of large scale investigations on the clinical use of streptokinase (SK) in patients with recent myocardial infarction were not available. The following considerations, although essentially speculative appeared to provide at that time a rational basis for a controlled trial of SK in this clinical condition

Apart from its antigenic effect, the only known action of SK was to activate the fibrinolytic system including the formation of a bovine plasminogen activator and transformation of human plasminogen to plasmin. The plasmin formed has a broad spectrum of activity causing not only lysis of fibrin and clots but also degradation of plasma proteins, such as fibrinogen, into break-down products. The reason for using SK as a therapeutic agent in the management of recent myocardial infarction had therefore to be found in either its fibrinolytic or its more general proteolytic action.

Associated with myocardial infarction, fibrin had been observed not only in the occluded coronary artery but also in the collateral circulation in the myocardium in thrombi forming in the cavity of the ventricle provoking perhaps peripheral emboli, and in the peripheral veins where thrombophlebitis, possibly complicated by pulmonary embolism, can occur However the weight of evidence for the presence of fibrin clots in each location was different and the possible action of SK should therefore be discussed separately

In patients who had come to autopsy after a recent myocardial infarction, thrombi had been found with various frequency *in the ventricular-cavity* of the heart, adjacent to the infarcted area. It may be assumed that they form after the onset of the myocardial damage. Although data on the frequency of such thrombi after a recent infarction in patients not coming to autopsy are totally lacking, they were to be a good substrate for the action of SK, because they are freshly formed and composed mainly of fibrin. One could question whether it is wise to lyse these clots. It is conceivable that lysis may be incomplete, and fragmentation with resultant embolism may occur If such emboli were not further lysed tissue damage could result. Secondly what would be the fate of thrombi which may form during the period of severe plasminogen depletion associated with the administration of high doses of SK ?

It is generally accepted that fibrin deposition plays an important role in *coronary artery occlusion*. However this can also result at least in part from an atherosclerotic plaque, a subendothelial haemorrhage or a platelet mass. So far in an individual case of recent myocardial infarction it is not possible even by coronary arteriography to determine the exact composition of the occlusion. Only in selected patients with infarcts namely those coming to autopsy it is feasible to investigate the coronary vessels and to learn the frequency with which fibrin is to be found The figures published by several authors vary widely (for references Van

de Loo 1963) between 13 and 74 per cent It is unlikely that a patient with a coronary artery occlusion due to subendothelial haemorrhage will benefit from treatment with SK The same expectation would also be valid in patients where the occlusion *mainly results from an atherosclerotic* plaque except when superimposed fibrin would be lysed in time by SK treatment It was even realised that coronary occlusion due to thrombus formation not in all cases would be lysed in time to avoid permanent myocardial damage

Fibrin has been described in the *collateral circulation* around a recent myocardial infarction. It is possible that thrombolytic therapy could be advantageous in myocardial infarction by opening (partly) occluded collaterals.

Finally in patients with myocardial infarction clots can occur at different *places outside the heart* probably most important for the patient s survival are thrombi in peripheral veins, since they may result in pulmonary embolism. An increased survival rate in patients with myocardial infarction treated with SK could be to a reduction in mortality caused by complication.

Since fibrin is not the only substrate for plasmin, we will now consider the possible beneficial effect of the action of plasmin *on other plasma proteins.* As already mentioned plasmin lyses fibrinogen and some other plasma proteins. It is not known to what extent lysis of plasma proteins could lead to a decrease in blood viscosity and therefore to a reduced resistance to blood flow in severely narrowed blood vessels. Through the action of plasmin on fibrinogen, different split products are formed their possible importance in the treatment of myocardial infarction *will now be considered Split products have* been studied extensively both in vitro and in vivo The in vivo action of different split products was known to include

- inhibition of polymerisation of fibrin and prolongation of the thrombin time
- *anti-thromboplastic activity*

Additional experimental work published *more recently has demonstrated that in* vitro the fibrinogen split products inhibit the platelet aggregation and adhesiveness (Wilson, McNicol and Douglas, 1968) Furthermore Poliwoda (1967) has reported preliminary results of animal experiments, suggesting that if animals are pretreated with purified anti-thrombin VI a thrombus formed after intimal damage is smaller than in the control animals The possible beneficial effects of split products in patients treated with SK for a recent myocardial infarction should be considered an attrac*tive hypothesis. Finally during completion* of this study several reports on the clinical *efficacy of SK in recent myocardial infarc*tion have been published and will be reviewed in the discussion

The purpose of the work reported here was primarily to investigate in a controlled study whether SK improves the short term outcome in patients with a recent myocardial infarction and not to test the validity of previous considerations. The present protocol was the result of experience gained in a previous unpublished trial, *conducted in several medical centres.* * In short patients admitted in different Eu-

In addition t some of the investigators of the present trial, we gratefully acknowledge the cooperation of Prof D H Demolin (Brussels) Dr. H. Kesteloot (Brussels) Dr A.H J Koops (Rotterdam) Dr A J Klomp (Rotterdam), Prof Dr E. Lavenne (Louvain), Prof Dr R. Masure (Louvain) Dr H Meyer (München) Prof D R Pannier (Gent) Dr R. Reuben (Brussels) Dr J Salmon (Liège), Prof Dr H Van Cauwenberghe (Liège) and Dr O Van Houte (Brussels)

ropean centres with a recent (72 hours or less) myocardial infarction were selected (see below) *Using a random sampling* technique the patients were divided into two groups one group was treated with SK and the other with heparin. Both groups received coumarin drugs. The criteria used to compare the results of the two treatments were primarily the mortality rate and also serial E.C.G. tracings and transaminase studies. Further data were required to study the side-effects of the drugs to ascertain that both groups were comparable at the start to ensure that both treatments were properly administered and to confirm that the contra-indications were identified and carefully respected by the investigators.

Pre-selection of patients

On admission to the department patients were considered as candidates for this study according to the following criteria

– *Positive criteria* suggesting inclusion in the study

1 the patient must have a *myocardial infarction* the diagnosis was made by each cardiac department or staff members according their own criteria * Patients with a second myocardial infarction could be included

2 the myocardial infarction must be *recent* viz. the time-interval between the onset of acute symptoms and commencing treatment with heparin or SK must be 72 hours or less. This time interval had to be carefully recorded

Negative criteria, necessitating exclusion from the study

1 diastolic pressure more than 100 mm Hg on admission or at any time until the start of heparin or SK treatment or grade III retinopathy or more (Keith–Wagener Barker)

2 diabetes mellitus

3 potential bleeders
 – of local origin recent or active gastro-intestinal ulceration or within the first three days after major surgery
 – generalised bleeding haemophilia, thrombocytopenia etc

4 Administration of coumarin or heparin since the onset of the present infarction resulting in marked prolongation of the prothrombin time" or clotting time

5 previous intensive parenteral SK treatment

6 serous impairment of hepatic or renal function

7 an expectation that permanent and controlled coumarin treatment for at least 3 months after the acute infarction would not be possible

8 age as such was not a limiting factor

Initial diagnostic tests and treatment

Patients meeting these criteria were thus pre-selected for inclusion in the study and were expected to receive the routine treatment for myocardial infarction as soon as possible It was not felt possible to standardise this treatment for all the collaborating centres

Blood analysis for fibrinogen thrombin time Quick s test Owren s test and plasminogen were not done at each centre instead plasma samples were deepfrozen and sent to the central laboratory in Leuven for analysis. This decreased the work for each centre and removed the need to wait for the results of these tests before

For the second analysis (see page 22) the diagnosis was made retrospectively in collaboration with two expert (Prof G Strom and D G Graf department of clinical physiology Uppsala) who reviewed the electrocardiogrammes ignoring to which treatment group the patients belong. This part of the study will be reported seperately

starting treatment It was also hoped that the results would become more homogeneous.

Selection of patients for treatment with SK or heparin

After pre-selection SK or heparin treatment was decided by opening serially numbered envelopes in which heparin or SK therapy was specified according to a random sampling technique For each collaborating centre each group of ten patients included a random distribution of 5 heparin and 5 SK specifications the latter was not known to the different investigators.

Heparin and SK treatment

100 mg heparin (= 2 ml) was diluted in a bottle containing 150 ml of 5 % glucose Then 25 mg prednisolone was injected intravenously and the first bottle of heparin-glucose was infused during a 30 minutes period The time of starting this infusion was recorded as "time zero" Infusion of a second bottle of 500 ml glucose 5 % containing 150 mg heparin immediately followed the first and the rate of flow was adjusted to run over a 12 hour period After 12 hours a third bottle identical to the second bottle was started Continuous intravenous infusion lasted 72 hours, every 12 hours a fresh bottle of 500 ml 5 % glucose with 150 mg heparin was used Each day 25 mg prednisolone was given intravenously for the first three days.

In the SK group thrombolytic treatment was initiated by the intravenous administration of a loading dose fixed at 1,250,000 units SK dissolved in 150 ml glucose 5 % The time of starting this infusion which was to last 30 minutes was recorded Just prior to starting this infusion 25 mg prednisolone were injected intravenously through the tube of the infusion set A second bottle with 500 ml glucose 5 % Containing 1,250 000 units SK was given immediately after the first The infusion was run at about 8 10 drops a minute with this rate the 500 ml bottle was empty after approximately 12 hours (which corresponds to 104 000 units SK/hour) The infusion of this maintenance dose was continued for the 72 hours of thrombolytic treatment and each day 25 mg prednisolone was given intravenously for the first three days. If excessive bleeding occurred the SK infusion was stopped and epsilon aminocaproic acid 8 gram injected intravenously followed by a bottle containing the same quantity and delivered over 8-12 hours.

In the two groups blood samples for leucocytes, transaminases etc and for coagulation and fibrinolysis studies were obtained just prior to and 30 minutes after the end of the infusion of the first bottle and subsequently at least once a day One blood sample was also taken for coagulation and fibrinolysis tests the day after the end of SK or respectively heparin administration.

Control during the first three days

Electrocardiographic tracings were obtained twice a day Daily blood samples were also taken for the determination of the following parameters haematocrit val-

SK was kindly supplied by H Dahlstrom M D Kabi, Stockholm, to whom we are indebted for support and help in the organization of this study

ue serum transaminases, erythrocyte sedimentation rate creatine phosphokinase leucocyte count

Coumarin treatment and the end of the heparin or SK treatment

In both groups (heparin or SK treatment) coumarin drugs were started 48 hours after "time zero" thus, for 24 hours the patients in the heparin group received a combined heparin-coumarin treatment and the patients in the SK group a combined SK-coumarin treatment During that time Quick's test or the Thrombotest R were determined daily Coumarin treatment was modified according to the results of these tests. Seventy two hours after "time zero the heparin or SK infusion was stopped

Thereafter coumarin treatment had to be continued for at least three months. The aim was to give a coumarin dose large enough to bring the Thrombotest R value between 10 and 25 %

Blood sampling was performed at repeated intervals and its timing is indicated in the section results.

1 Each blood sample *for coagulation and lysis tests* at the central laboratory in Leuven was collected in two tubes

a. 4 9 ml blood + 0 1 ml citrate 160 g/l The blood was immediately centrifuged and the plasma deep frozen

b 4.5 ml blood + 0 4 ml Trasylol R solution (= 400 units) + 0 1 ml citrate 160 g/l The blood was immediately centrifuted and the plasma deep frozen.

At the end of thrombolytic or heparin therapy all the deep frozen plasma samples were sent to the central laboratory in a suitable box containing dry ice

The plasma fibrinogen level was there determined on the plasma with Trasylol R using the Fibrin Polymerization Time (F.P T) test of Vermylen, De Vreker and Verstraete (1963) The plasminogen concentration was determined on the plasma without Trasylol R using the method of De Vreker (1965) the normal value averaging 5 000 U/ml.

2 Other tests such as haematocrit leucocyte counts, serum transaminases, erythrocyte sedimentation rate creatine phosphokinase, were performed in the laboratories of the different collaborating centres, the comparability of the results was not investigated

The data from the different centres, including the electrocardiogramms, were collected for each patient in a specially designed chart at the patients discharge from the hospital the chart together with the deep frozen plasma samples was sent to the coordinating centre in Leuven where the results of the coagulation and lysis tests were added

The electrocardiogrammes were then analysed separately by two experts, who did not know to which treatment group the patients belong and the evaluation of all data was performed using an IBM Quest programme run on a 1440 IBM machine.

RESULTS

The charts of 192 patients were completed and returned to the coordinating centres in Leuven However all charts (n = 24) from centres where less than 10 patients were treated were not used in the analysis one further chart was dropped out because the patient received heparin although he was scheduled for the SK group All other charts (n = 167) were included in the first analysis 83 being in the SK and 84 in the heparin group

1 First analysis

Before evaluating the results of therapy in these patients we will try to demonstrate that the groups were comparable in other respects.

a) Comparability on admission into the study

The patients of both groups were evaluated according to various criteria some of them being known to influence the outcome of patients with myocardial infarction. The results of this evaluation are given in table 0

TABLE 0 Characterisation of both groups before treatment (first analysis)

			Hep	SK	p
– total number of patients		n	84	83	
– age of the patients (in years)		m	59.2	58 4	
		SD	11.5	10 1	
		n	84	81	
– sex	male	n	75	73	
	female	n	9	10	
body weight (in kg)		m	73 9	71.5	
		SD	8 7	11.0	
		n	53	47	
cerebrovascular accident before the		+ n	6	1	> .05
present infarction		– n	71	75	
atherosclerotic disease of peripheral		+ n	11	10	
arteries		n	66	67	
– diabetes mellitus		+ n	7	8	
		– n	71	71	
– previous hypertension		+ n	3	9	> .05
		– n	68	65	
previous infarction		– n	71	71	
		+ n	10	9	

		Hep	Sk	p
– angina before the present infarct	+ n	40	45	
	n	40	35	
– non atherosclerotic heart disease	+ n	0	0	
	n	79	78	
– other diseases	+ n	12	7	
	n	68	73	> .05
– time interval between onset of pain and start of therapy (in hours)	m	22.5	20 1	
	SD	19.8	10.3	
	n	79	79	
heart failure	+ n	10	8	
	– n	73	73	
– shock	+ n	9	10	
	– n	75	71	
– arrhythmia	+ n	10	17	
	– n	72	64	
– friction rub	+ n	1	2	
	– n	8	79	
– retrosternal pain	+ n	74	71	
	– n	7	5	
– recent embolus	+ n	0	0	
	– n	83	81	
– systolic blood pressure (in mm Hg)	m	133 0	129 5	
	SD	25.5	25 5	
	n	80	74	
– diastolic blood pressure (in mm Hg)	m	84 4	81.8	
	SD	17.0	14 3	
	n	80	73	
– pulse rate (in beats per minute)	m	86 2	83 5	
	SD	19 5	18.0	
	n	78	76	
– temperature (°C)	m	37 2	37 1	
	SD	0 65	0 71	
	n	74	71	
– serum G.O T (Wroblewski units)	m	83.8	82.0	
	SD	95.6	78.6	
	n	71	68	
	m $\log_{10}$x	1 680	1 737	
	SD $\log_{10}$x	0 450	0 438	
	antilog m $\log_{10}$x	47 9	54.6	
– creatine phosphokinase (CPK) (micromole/litre serum/hour)	m	4 2	3.87	
	SD	6 38	5 13	
	n	60	59	
haematocrit	m	44.0	45.3	
	SD	4 4	4.6	
	n	64	59	

		Hep	SK	p
leucocyte count	m	12,400	13 720	
	SD	4 180	6 630	
	n	62	60	
erythrocyte sedimentation rate (mm after 1 hour)	m	16.5	13.3	
	SD	18.0	18 9	
	n	64	60	
	m $\log_{10}x$	1 013	0.853	
	SD $\log_{10}x$	0 435	0 471	
	antilog m $\log_{10}x$	10.3	7 13	
– serum cholesterol (mg %)	m	267.5	254.3	
	SD	58.0	49 2	
	n	46	57	
– transmural infarction	n	73	7	
mainly anterior infarction	n	40	41	
mainly posterior infarction	n	40	36	

In this table "+ n" means number of patients with a positive answer to this question.
– n" means number of patients with a negative answer to this question.

For some parameters the number of positive and negative answers for each group is ess than the total number of patients in the heparin (84) or SK (83) group because the answer to that question was not available in the patient s chart For quantitative data such as age, body weight etc the number of patients in each group for which the data are available is each time indicated after the symbol n *

As can be seen from table 0 for the criteria evaluated here only very small differences are found between the heparin and the SK group and when calculated none of these differences was significant The nature of the other diseases which were present on admission to the study was

for the heparin group

syphilis
– gallstones
– pernicious anaemia
– eczema
– gout
– peptic ulcer (not recent)
– chronic bronchitis and emphysema (three patients)
– dysproteinaemia
– hyperlipaemia
– obesity

for the SK group

– psoriasis
– pernicous anaemia
– prostatic carcinoma
– polycythaemia vera
– bronchopneumonia
– urinary tract infection
– sigmoid colon carcinoma

For some parameters the mean value was exceeded by the standard deviation" this is particularly the case for serum GOT CPK and sedimentation rate and suggests that the distribution of the results for these parameters is not Gaussian It is unlikely to

be due to the different units, since all results were expressed in the same units. It could be thought that the heparin and SK groups were composed of different subgroups indeed the patients could have infarcts of different magnitude and could be admitted into the trial at any time during the first 72 hours after the onset of the acute symptoms. The values of the serum GOT CPK and sedimentation rate are known to vary during the first days after infarction. For the serum GOT values and the sedimentation rate a Gaussian distribution was obtained when the results were translated into logarithms The logarithmic values are also shown in the table and are referred to as mean $\log_{10} x$ and standard deviation of $\log_{10} x$ For the CPK a normal distribution could not be obtained even by using this approach therefore no further statistical analysis of CPK values in made

Since patients were allocated blindly to one or other treatment and since no significant differences were found between the two groups, they may be considered comparable

b) *Complications before the start of infusion*

Once an envelope designating treatment was opened the patient was considered to have been admitted into the study In fact 3 patients died between admission into the study and the start of the infusion 2 were scheduled for SK and one for heparin treatment

c) *Evaluation of the infusion period*

SK or heparin was infused for 72 hours.

New complications were noted and specific questions concerning complications known to occur in association with heparin or SK therapy were asked in the protocol The complications noted are recorded in table 1 This shows that several complications were slightly more frequently observed during the SK than during the heparin treatment rigor shock bleeding, back pains. However none of these differences reach a sufficient level of statistical significance when tested with the two-tailed chi square test For each group all patients with one of the listed complications were added to those who developed a temperature rise of at least 1 C to obtain the total number of patients developing new complications during the infusion period The slightly higher complication rate in the SK group compared to the heparin treated group was not significant The nature of the bleeding complications was also specified In the 9 patients who bled during the SK infusion, bleeding occurred twice from the nose only and twice only at the puncture site In one patient nose bleeding, bleeding at puncture site and spontaneous haematomata were noted at the same time 3 patients developed one of the following complications spontaneous haematoma macroscopic haematuria and melaena (the patient had a sigmoid colon carcinoma) In one SK treated patient the nature of the bleeding was not further specified

In the 4 patients who bled during the heparin infusion the localisation was different at each occasion and restricted either to bleeding at puncture sites, or haemoptysis, or haematemesis (the patient had a peptic ulcer) or melaena

In a further attempt to evaluate bleeding in the SK group we studied the evolution of the haematocrit in this group compared to the heparin treated group Table 2 shows the mean and standard deviation of the haematocrit from all patients, where those results were available on the following three occasions before treatment 4 and 7 days after the start of infusion

TABLE 1 Complications during the infusion period (first analysis)

		Hep	SK	p
– death	n	3	4	
– rigor	+ n	1	6	> .05
	– n	45	50	
– rash	+ n	0	1	
	– n	46	55	
shock	+ n	9	14	> .05
	– n	35	4?	
– bleeding	+ n	4	9	> .05
	– n	35	42	
– new precordial pain episode	+ n	0	1	
	– n	46	55	
mental disturbances	+ n	0	1	
	n	46	55	
back pain	+ n	0	7	
	– n	46	49	
arthralgia	+ n	0	1	
	– n	46	55	
temperature rise of more than 1 degree centi grade without other complications	+ n	31	16	
total number of patients with new complications	+ n	45	56	> .05
	n	37	23	

Table 2 shows that the haematocrit ore the start of the infusion and at different times after the infusion was somewhat different in the SK compared to the heparin group these differences were however not statistically significant ($p > 0.1$) Using the method of paired comparison it can be shown that the haematocrit decrease between the value taken before and seven days after the start of infusion was not significant in the heparin group ($p > 0.1$) but highly significant ($p < 0.001$) in the SK treated group. However the difference in decrease in haematocrit between the SK and heparin treated group was no longer significant ($p > 0.1$)

TABLE 2 Progress of haematocrit value (only patients of the first analysis with sufficient data)

Blood sample	Hep (n=.3) m ± S D	SK (n=?6) m ± S D	p
Before start of infusion	42.8 ± 6 3	45 ? ± 3 9	> 0 1
4th day	42 1 ± 6 4	41 9 ± 4.3	
th day	4 1 ± 6 0	40 4 ± 4 ?	> 0 1
p between time 0 and 7th day	> 0 1	< 0.001	

TABLE 3 Progress of haematocrit values (first analysis)

Blood sample	Hep n	Hep m ± S.D	SK n	SK m ± S.D	p
– Before start of infusion	64	44 0 ± 4 4	59	45.3 ± 4.6	>0 1
– 1st day	62	44.5 ± 4.5	62	46.0 ± 5.5	>0 1
– 2nd day	61	43 1 ± 5.5	66	44 7 ± 5.3	>0.1
3rd day	50	42.6 ± 5.2	58	43 7 ± 4.3	>0 1
– 4th day	44	42.6 ± 4 9	44	42.9 ± 4 6	>0 1
– 7th day	29	42.6 ± 5 9	32	40.5 ± 4.2	>0 1
– 14th day	21	40 6 ± 5 1	20	39 4 ± 4 4	>0 1
– 21st day	15	40 9 ± 6.0	17	40 7 ± 3 8	>0 1

Performing this kind of analysis, a patient who for instance was bleeding during the SK infusion and who died on the fifth day would have been excluded since the haematocrit on the 7th day would not have been available We therefore studied the progress of the haematocrit taking into account all values available. These results are shown in table 3 Again no significant difference between the SK and the heparin group was found

d) *Accuracy of the infusions*

In comparing two kinds of treatment it is necessary to ensure that these treatments were given as scheduled As mentioned earlier one patient who was due to receive SK received in fact heparin treatment and was not included in the first analysis. A question in the protocol asked if the patient was treated exactly according to the proposed infusion scheme In the heparin group the infusion scheme as described was stated in the chart to be followed in 67 patients but not followed in 16 and 1 patient scheduled for heparin treatment died before the start of infusion. In the SK group the infusion schedule was reported to have been followed in 69 but modified in 11 patients, for 1 patient no answer to this question was obtained and 2 patients scheduled for the SK treatment died before the start of SK infusion.

Blood was collected at different moments during treatment just before after the initial dose and subsequently once a day (mostly in the morning) during the infusion period The blood samples were deep frozen and sent to Leuven where the following analyses were made on each sample fibrinogen (using the F P T test) thrombin time Quick s test Owren s test and plasminogen determination.

In the SK treated group the plasminogen determinations were used as an indication that the patient did receive SK in the agreed dose. We considered that a patient had received enough SK if the plasminogen level was 200 U/ml or less in all, or all but one samples. Complete data are available in only 61 SK treated patients and according to these criteria 51 of them received enough SK In the other 10 patients the plasminogen level during treatment was higher than 200 U/ml in more than 1 sample.

For the heparin treated patients, the only test available to evaluate the anticoagulant effect of the heparin was the thrombin time Sufficient thrombin time

determinations were available in only 37 heparin treated patients. The thrombin time was more than twice the normal value in all plasma samples taken during the infusion in only 16 patients. This suggests that the control group as a whole was probably only very slightly anticoagulated

The results of the fibrinogen determination with the F P T test are given in tables 4 and 5

This shows that in the heparin treated patients, there is a small tendency for fibrinogen to increase during the infusion period In the SK treated patients there is a fall in fibrinogen and a late increase Since a standard initial dose of SK was given to all patients, the influence on the plasma fibrinogen level could be different because of the difference in SK inhibitors in the

TABLE 4 F.P T test at different times in SK treated patients (first analysis)

F.P T fibrinogen mg % (plasma)	Before (n)	Number of cases with a given F.P T value After initial dose (n)	1st day (n)	2nd day (n)	3th day (n)	After therapy (n)
0 49	0	19	25	17	6	7
50 99	0	2	0	1	2	2
100 149	2	1	7	10	5	6
150 199	3	1	7	7	4	3
200 249	8	3	1	2	4	2
250 299	10	2	1	2	1	2
300 349	4	1	0	0	2	0
350 399	9	2	2	0	2	2
400 449	4	0	1	0	4	2
450 499	0	0	0	1	1	0
500 549	2	1	0	2	1	2
550 599	2	0	1	0	7	3
> 600	0	0	0	0	1	1
All values	44	32	45	42	40	32

TABLE 5 F.P T test on samples from heparin treated patients from the first analysis

Sample specification	Number of samples	Fibrinogen in mg % m ± S.D
– Before infusion	37	352.0 ± 138 0
After initial dose	29	337.5 ± 153.5
– First day after start	27	382.9 ± 125.5
– Second day after start	23	418 4 ± 129.3
– Third day after start	25	421.2 ± 167.0
– At the end of the infusion	17	417 1 ± 160 1

population. The maximum fall was in some cases noted in the sample drawn after the initial dose, while in others only in later samples. In the later samples, the distribution of the fibrinogen concentration was not Gaussian since the fibrinogen increase started early in some and late in other patients thus, no "mean" and "standard deviation" were calculated table 4 gives only the frequency distribution in the SK treated group

e) Hospital death rate

Of the 167 patients admitted into the study and included in the first analysis, 35 died in hospital The time of death for patients in each group is given in table 6

Table 6 shows that for almost every interval of time considered the death rate is slightly higher in the SK group compared to the heparin treated group however none of these differences reached a suf

TABLE 6 Hospital death (first analysis)

Moment of death	Hep (n)	SK (n)	P
– Before the start of infusion	1	2	
– During the first 4 hours of infusion	1	3	
– Between 24 and 72 hours of infusion	2	1	
– Late hospital death	11	14	
– Total hospital death	15	20	> 0.05
Number of patients admitted in the first analysis	84	83	

TABLE 7 Causes of death (first analysis)

Cause of death	Hep (n)	SK (n)
– Arrhythmia	2	2
– Heart rupture (a)	2	6
– Septal perforation (a)	0	1
– Lung embolism (a)	1	0
– Cerebral haemorrhage (a)	0	1
– Cerebral embolism (a)	1	0
– Unknown	9	10
All causes	15	20

(a) = confirmed at autopsy

TABLE 8 Late complications (first analysis)

Nature of complications	Hep (n)	SK (n)
– Shock	6	5
– Heart failure	3	1
– Reinfarction	0	0
– Peripheral embolism	0	1
– Arrhythmia	5	6
Friction rub	0	1
Aneurysm	0	1
Total number	14	15

TABLE 9 Progress of erythrocyte sedimentation rate (first analysis)

Blood sample	Heparin			SK			P
	n	m $\log_{10}x$ ± S.D.$\log_{10}x$	antilog m $\log_{10}x$	n	m $\log_{10}x$ ± S.D.$\log_{10}x$	antilog m $\log_{10}x$	
Before infusion	64	1.013 ± 0.435	10.3	60	0.853 ± 0.471	7.1	> 0.05
1st day	57	1.136 ± 0.467	13.7	54	0.69[illegible] ± 0.433	4.9	< 0.001
[illegible]nd day	59	1.369 ± 0.358	23.4	61	0.759 ± 0.444	5.7	< 0.001
3rd day	54	1.510 ± 0.[illegible]	32.4	57	0.886 ± 0.456	7.7	< 0.001
4th day	5[illegible]	1.5[illegible]6 ± 0.384	33.6	53	1.011 ± 0.456	10.3	< 0.001
7th day	5[illegible]	1.530 ± 0.344	33.9	5[illegible]	1.388 ± 0.450	24.4	> 0.05
14th day	46	1.445 ± 0.3[illegible]0	27.9	45	1.469 ± 0.407	29.4	> 0.1
[illegible]1st day	38	1.371 ± 0.315	23.5	45	1.410 ± 0.331	25.7	> 0.1

TABLE 10 Progress of serum GOT (first analysis)

Blood sample	Heparin			SK			P
	n	m $\log_{10}x$ ± S.D.$\log_{10}x$	antilog m $\log_{10}x$	n	m $\log_{10}x$ ± S.D.$\log_{10}x$	antilog m $\log_{10}x$	
Before start of infusion	71	1.680 ± 0.450	47.9	67	1.737 ± 0.438	54.6	> 0.1
1st day	75	1.959 ± 0.387	91.0	70	1.978 ± 0.463	95.1	> 0.1
2nd day	73	1.834 ± 0.4[illegible]4	68.[illegible]	73	1.937 ± 0.364	86.5	> 0.1
3rd day	65	1.680 ± 0.456	47.9	7[illegible]	1.725 ± 0.3[illegible]9	53.1	> 0.1
4th day	59	1.546 ± 0.395	35.[illegible]	63	1.598 ± 0.381	39.6	> 0.1
7th day	56	1.417 ± 0.[illegible]90	26.1	50	1.537 ± 0.280	34.4	0.05 > p > 0.0

ficient level of significance ($p > 0.05$) when calculated with the chi square two-tailed test The causes of death are listed in table 7 If the patient died in heart failure or shock and no direct cause was found even at autopsy the cause of death was listed as unknown. Considering only the patients subjected to autopsy ($n = 22$) heart rupture and septal perforation was slightly more frequent as the cause of death in the SK (7/12) than in the heparin group (2/10) this difference was however not significant ($p > 0.05$)

f) *Late complications*

Later whilst in hospital and after the end of the infusion, complications were noted in 36 patients who received SK and 26 patients who received heparin. In most of the cases the only complication noted was a temperature rise of more than 1 C (21 patients in the SK group and 12 in the heparin group) other complications are listed in table 8 No continuous monitoring was used to measure arrhythmia so the true incidence was higher

g) *Progress of the erythrocyte sedimentation rate*

The erythrocyte sedimentation rate was measured daily during the first four days and thereafter weekly for the first 3 weeks. The results are expressed in millimetres after one hour and shown in table 9 the mean and standard deviation was not calculated on these values, but on the logarithms of these values, since the latter correspond to a normal distribution. The antilogarithm of the mean of $\log_{10} x$ is also given.

Table 9 shows that the sedimentation rate in the heparin treated group increased during the infusion period in the SK treated group the sedimentation rate decreased during the infusion period and increased thereafter to a level comparable with that for the heparin treated group

The influence of in vitro addition of SK or heparin on the sedimentation rate has been studied elsewhere (Amery 1969) These experiments showed that the decrease in sedimentation rate was not related to the SK concentration per se but to the plasmin concentration, the fibrinogen decrease and possibly to the presence of breakdown products.

It is likely therefore that the decrease of the sedimentation rate during SK therapy is due to the fibrinogen decrease and/or the presence of breakdown products.

h) *Progress of serum GOT*

The use of current statistical methods was possible when the serum GOT values were used as the logarithm of the values in Wroblewski units. The results are shown in table 10

Neither before nor during the first four days was a statistically significant difference found in the serum GOT values (expressed as logarithmic values) between the heparin and the SK treated group By the seventh day a higher serum GOT level was found in the SK compared to the heparin treated group however if one corrects for the slightly higher serum GOT values before the start of the infusion in the SK compared to the heparin group this difference does not reach a sufficient level of significance ($p > 0.05$) The relatively low serum GOT values in these groups could be due to the fact that some of the patients included probably did not have a myocardial infarction as will be discussed in the second analysis.

Conclusion of the first analysis

Patients diagnosed in different centres as having a recent (< 72 hours) myocardial

TABLE 11 Hospital mortality in the second analysis

Mortality	Hep (*n*)	SK (*n*)
– Within 72 hours after start of infusion	3	1
– Later hospital mortality	5	8
– Total hospital mortality	8 (17.8 %)	9 (16.7 %)
Patients at risk	45	54

TABLE 12 Progress of serum GOT (second analysis)

Blood sample	Heparin			SK			p
	n	$m \log_{10}x \pm$ S.D.$\log_{10}x$	antilog $m \log_{10}x$	n	$m \log_{10}x \pm$ S.D.$\log_{10}x$	antilog $m \log_{10}x$	
Before start of treatment	76	1.585 ± 0.464	38.5	35	1.611 ± 0.366	40.8	> 0.1
1st day	23	2.049 ± 0.481	112.0	35	2.010 ± 0.444	102.4	> 0.1
2nd day	22	2.007 ± 0.3[illegible]	101.7	38	2.031 ± 0.330	107.4	> 0.1
3rd day	19	1.827 ± 0.271	67.2	37	1.844 ± 0.335	69.9	> 0.1
4th day	19	1.675 ± 0.294	47.3	33	1.765 ± 0.298	58.[illegible]	> 0.1
7th day	20	1.404 ± 0.387	25.4	26	1.614 ± 0.285	41.1	0.05 > p > 0.01

TABLE 13 Progress of erythrocyte sedimentation rate (second analysis)

Blood sample	Heparin			SK			p
	n	$m \log_{10}x \pm$ S.D.$\log_{10}x$	antilog $m \log_{10}x$	n	$m \log_{10}x \pm$ S.D.$\log_{10}x$	antilog $m \log_{10}x$	
Before start of infusion	23	0.949 ± 0.508	8.9	29	0.829 ± 0.404	6.7	> 0.1
1st day	19	0.951 ± 0.506	8.9	28	0.655 ± 0.428	4.5	0.05 > p > 0.0
2nd day	17	1.[illegible]45 ± 0.245	17.6	31	0.708 ± 0.396	5.1	< 0.001
3rd day	18	1.496 ± 0.334	31.3	30	0.804 ± 0.43[illegible]	6.4	< 0.001
4th day	18	1.511 ± 0.391	32.4	[illegible]7	0.917 ± 0.480	8.3	< 0.001
7th day	17	1.508 ± 0.326	3[illegible].2	27	1.436 ± 0.427	[illegible]7.3	> 0.1
14th day	13	1.404 ± 0.235	25.4	[illegible]1	1.59[illegible] ± 0.37[illegible]	39.1	> 0.1
21st day	10	1.4[illegible]5 ± 0.234	26.6	22	1.420 ± 0.297	26.3	> 0.1

infarction were treated randomly with heparin or SK In 167 cases from 8 different centres the randomisation was considered valid to allow of a first analysis 84 patients were treated with heparin and 83 with SK

When comparing the two groups, no difference in the effect of several para meters which might influence the course of a myocardial infarction was found

No significant difference could be found between the groups for mortality in hospital, or for serum transaminase, when measured at various times after the start of therapy During the infusion period, the sedimentation rate increased in the heparin treated group but decreased in the SK treated group

2 Second analysis

The study of Schmutzler Heckner Körtge Van de Loo Perzold Poliwoda, Praetoriu and Zekorn (1966) showed that there was a significant reduction in the hospital mortality after SK treatment compared to a control group if one considers patients treated within the first 12 hours, especially if one excludes the patients who died within the first hours after the start of treatment.

In the second analysis of our data we will consider only patients treated within the first 12 hours after the onset of symptoms.

We have excluded all patients (n = 3) who died before the start of the infusion and all patients (3 heparin treated and 5 SK treated) with doubtful diagnosis. In these, the serum enzymes were not elevated and the electrocardiograms were classified as normal or doubtful by an expert who reviewed the tracings ignoring to which treatment group the patient did belong. The patients excluded from the first analysis were also excluded here, leaving 99 patients who fulfilled the criteria 45 were treated with heparin and 54 with SK The hospital mortality for the two groups is given in table 11

No significant difference in mortality was found between the SK treated patients and the control group the number of patients remains however low

In the first analysis the distribution of the erythrocyte sedimentation rate, CPK and serum GOT was not normal one possible explanation was a difference in the age of the infarct when the infusion started In the second analysis the age limits were narrower (less than 12 hours) but again the distribution was not normal for these three parameters. It is therefore unlikely that a variation in the age of the infarct could explain completely the abnormal distribution. By transferring the values for the erythrocyte sedimentation rate and serum GOT into logarithms a normal distribution was obtained Table 12

TABLE 14 Hospital mortality (third analysis)

	Hep	SK with low plasminogen	SK others
Hospital mortality	8 (17.8 %)	4 (15 %)	5 (18 %)
Patients at risk	45	27	27

shows that at no time was the serum GOT concentration significantly different in the SK treated patients when compared with the heparin group The sedimentation rate (table 13) followed the pattern described for the first analysis.

3 Third analysis

In this analysis the SK treated group defined in the second analysis, was subdivided into two groups those who were given enough SK to keep the plasma plasminogen level below 200 U/ml during the infusion period and the other SK treated patients (table 14) The mortality in those two subgroups is compared to the mortality in the heparin treated group as defined in the second analysis No significant difference was found

DISCUSSION OF THE VALUE OF SK IN THE TREATMENT OF RECENT MYOCARDIAL INFARCTION IN MAN

Although the effectiveness of SK has been evaluated in acute experimental myocardial infarction in animals (Hiemeyer and Rasche, 1968) these results are not reviewed here since the present discussion is limited to trials in patients with recent myocardial infarction

Firstly the criteria for evaluation of a therapeutic trial in myocardial infarction will be discussed. Then these criteria will be applied to the trial presented above and to those published in the literature

A. Description of the criteria for evaluation of a therapeutic agent in recent myocardial infarction

1 *Selection of the patients*

Even if the criteria for selection are clearly defined and carefully followed part of the selection is outside the control of the investigators. Thus, some patients with recent myocardial infarction will never be admitted to the hospital indeed some infarcts were "silent" and not diagnosed at the moment of infarct the admission policy for patients with a diagnosed infarct can vary from area to another thereby influencing "spontaneous selection. Some local medical doctors do not favour hospitalisation for very recent myocardial infarction and some patients die before admission. Therefore selection takes place in a group of patients with a myocardial infarction, the composition of which is independent of the investigators.

Selection made by the investigator includes positive and negative criteria for *positive criteria,* the investigator has to define the minimum criteria for the diagnosis of infarction only clinical criteria ECG criteria serum enzymes etc How recent should the infarct be? Can a patient with a second or third infarct be admitted? If one selects only patients with a very recent infarct (less than 6 hours) it could be that the ECG alterations are not yet present and the serum enzymes not yet elevated furthermore, a myocardial infarction with a normal ECG is possible It is of some importance to investigate these kinds of patient when considering the evaluation of a drug which may be useful in the very early treatment of infarction If these patients are included however it must be appreciated that they represent a special group which preferably is stratified separately

Also the *negative selection criteria* should be defined carefully to exclude especially those patients in whom the use of either the new treatment or the control therapy is contraindicated. Because of hospital organisation, all patients admitted at night, during week-ends or at other times, may need to be excluded this should be the same for all patients and not only for one group The need for one particular doctor to be present before the start of therapy with the new drug could lead to a systematic error and arrangements should be made to avoid extra delay in starting therapy in the trial compared to the control group

Any conclusion as to efficacy of one or other treatment must be restricted to the categories of patients selected for study

2 *Allocation of the selected patients to the trial and control group*

When considering a disease such as myocardial infarction, in which the prognosis varies from patient to patient it may be useful to stratify patients according to parameters known to influence the prognosis. Such a stratification produces more homogeneous subgroups in which significant results for some subgroups may be obtained which might have been less apparent when considering the group of patients as a whole

After selection and perhaps stratification, patients should be allocated at random to the trial and control series. With drugs which completely change the prognosis of a disease, e.g. antihypertensive therapy in patients with malignant hypertension without severe renal insufficiency it is possible to use a group of comparable patients from a preceding period or from another institution as the control series provided the groups are sufficiently defined However preliminary studies (Fletcher Sherry Alkjaersig, Smyrniatis + Jick 1959) have shown that thrombo- agents are unlikely to change drama the outcome of the total population of patients with recent myocardial infarction. It is necessary to use therefore an accepted randomisation technique to allocate the selected and stratified patients to the trial or control series, i.e. each patient should have an equal chance to be placed in any one of the two treatment groups.

To admit patients alternately to the trial or control series is a procedure which is not beyond criticism, especially if the person who selects the patients knows to which series the patient is being allocated This could introduce an unconscious bias to the decision to admit or exclude a patient If all patients admitted to hospital are included in the study alternate distribution is acceptable for thrombolytic therapy however certain patients have to be excluded

Another system for allocating the selected patients to the experimental or control group is the closed envelope system, in which the contents of each envelope determine the patient s allocation. The envelope can be prepared either by using a specially prepared series or by tossing a coin. However a long series of the same treatment should be avoided because, after a series of several (e.g. 7) patients have been treated successively with drug A, something could change in the prognosis of myocardial infarction without being noticed by the investigator (e.g. changed atmospheric donditions, better nursing, etc ..) if then a series of patients has to be treated successively by drug B this could introduce a systematic error

Even if the patients are allocated at random to the experimental and control series, it is still necessary to show that both series are in fact comparable the bigger the series, the greater the chance they will be. If the number of patients joining the trial and control series differs significantly especially in long series, it is unlikely that the randomisation has been carefully planned and followed

Not only the number but also the nature of both series of patients should be compared in the evaluation in the treatment of acute myocardial infarction it is necessary to demonstrate that the effect of parameters known to influence the prognosis is the same in both series e.g. shock frequency of arrhythmia etc ...

3 *Administration of the therapeutic agent*

Most studies clearly define how the drug under investigation has to be administered

and how the control series should be treated However one should be able to confirm that the patient did indeed receive the drug for which he was scheduled This is almost impossible without the careful collaboration of all investigators in the trial and it becomes even more difficult if many centres and many investigators are involved Several procedures can be helpful

Each investigator can be given a series of numbered sealed envelopes and asked to use for each new patient selected for the study the envelope with the lowest number of the stratification group to which he belongs. If the dates of starting the treatment do not match the number sequence, it is clear that this rule has not been followed and that each patient did not receive the number for which he was sheduled

Each centre collaborating in the study can be asked to keep a record of all patients admitted to the hospital with a diagnosis of the disease under study and to indicate why some patients with this disease were not admitted to the study

Probably the safest single blind system is to ask each investigator to call the coordination centre each time he has a patient for the study The coordinator can then obtain details about the patient and specify which drug is to be used

A double blind system in the evaluation of thrombolytic agents would be ideal but many investigators consider it dangerous – perhaps without reason – in recent myocardial infarction.

It is not only necessary to try to make sure that each patient received the scheduled treatment but also that it was given in the agreed dose. An indicator substance can be added to the drug or if the drug produces known changes in the blood one can follow these. For SK therapy the changes in plasma plasminogen level are a useful indicator since a marked decrease in the plasminogen level of a patient with a myocardial infarction is unlikely to be due to other factors than the administration of plasminogen activators, such as SK or urokinase Such measurements cannot only show that the drug was given but also at what level, which could be important in a comparison of different administration schedules of the same drug.

4 *Standardisation of other therapeutic procedures*

Other therapeutic procedures should not only be the same in the trial and the control series but also be defined as carefully as possible in order to allow comparison between several studies.

For example if rigourous treatment of heart failure and early mobilisation were to decrease the incidence of death due to thrombolic complications in recent myocardial infarction, the use of this kind of treatment in one study and not in another would introduce a different mortality rate into the two studies.

Failure of standardisation of other therapeutic procedures might explain results, which on first inspection could seem contradictory

5 *Follow-up and evaluation of the success rate*

Numerous criteria can be considered in the evaluation of a drug in recent myocardial infarction death rate, reinfarction rate progress of serum enzymes or ECG thromboembolic and bleeding complications, arrhythmia functional status, etc _ The observation period can be restricted to the time spent in hospital but should be defined Re-evaluation after a long term follow-up should be considered.

For certain criteria where the subjective interpretation of the Investigator could be important double blind evaluation could become essential This is possible even with highly active drugs such as thrombolytic agents. For other criteria a single blind technique can be considered as sufficient One part of the data can be evaluated separately on a double blind basis e g. the ECG tracings can be studied by a reader who does not know which therapy each patient received

The criteria which have been described above will now be applied to some studies *on the treatment of recent myocardial* infarction with SK published previously and to the present study

B Application of the described criteria on the therapeutic trials concerning the usefulness of SK in recent myocardial infarction

Studies on the use of urokinase or plasmin in the treatment of recent myocardial ion are only mentioned here De Bellet Tsitouris, Lecks and Sandberg 960) Dewar Horler and Cassels-Smith 1961) Richter Cliffton, Epstein, Musac chio Nassar Favazza and Katabi (1962) Datey Hansoti and Pandya (1962) Dewar Stephenson Horler Cassels Smith and Ellis (1963) Lippschutz, Ambrus, Constant Rekate, Collins and Sokal (1965) Also several papers on treatment with SK of acute myocardial infarction published without a control series will not be discussed (Sailer Wehrschutz and Tilz 1968 Poliwoda, Schröder and Hecker 1963 Schmutzler 1963 Haan and Tilsner 1963) Some of these reports are concerned primarily with the progress of blood fibrinolytic and coagulation parameters and are intended to demonstrate the feasibility of obtaining and sustaining a thrombolytic state in these patients (Fletcher Sherry Alkjaersig, Smyrniotis and Jick 1959)

Five german and a Swiss centres have compared in a large scale cooperative trial, SK and heparin treatment in patients with recent myocardial infarction. The different papers reporting each part of these results will now be discussed Schmutzler Heckner Körtge Van de Loo Pezold Poliwoda Praetorius and Zekorn (1966) reported on the clinical outcome of the total material collected in this trial 588 patients with a recent (less than 12 hours) myocardial *infarction were treated* 297 *with SK and* 261 with heparin In considering the total group the hospital mortality was slightly lower in the SK (14 1 %) compared to the heparin (21 7 %) treated group this difference reached a level of significance of $0\,05 > p > 0\,02$ Considering only the patients who died between the 2nd and 40th day the hospital mortality was significantly ($0\,02 > p > 0\,01$) lower in the SK (8 7 %) compared to the heparin (16 1 %) treated group The relative frequency of causes of death was about the same in the SK and the heparin treated group heart rupture occurred to the same extent in the SK ($n = 8$) compared to the heparin ($n = 9$) treated patients. The difference in thrombo-embolic complications between the SK (5 4 %) and the heparin treated group (7 3 %) was not significant

The following comments * can be made

1 The SK treatment in these studies was reported to be given at two different schedules either a single initial dose was given calculated according to the patient s SK resistance or 250 000 units SK were given and if after the in vitro determina-

* We are indebted to Priv-Doz. Dr Van de Loo for reviewing these comments concerning their study

tion of SK resistance the calculated initial dose requirement appeared to be higher than 250,000 units, an additional amount of SK was administered The results of the two modes of SK treatment were not considered separately

2 The patients were first divided in an (A) early (3 hours or less) and a (B) late (4-12 hours) treatment group All patients of group A (n = 194) were treated with SK and at the end compared with another group of patients (n = 81) treated with heparin within the first 3 hours. These 275 patients were not allocated randomly to the heparin or SK treated group The late treated patients (group B) were treated alternately with SK or heparin apart from the theoretical objection against alternate treatment, it is unlikely that this procedure has been followed strictly in group B since at the end, in this group 180 patients were treated with heparin and only 103 with SK. The authors emphasised in their paper that no strict randomisation was achieved but felt that this should not invalidate their conclusions since they did not find a significant difference between the SK and heparin treated groups concerning age and sex distribution, localisation of the infarct and early mortality However it is likely that additional factors influence the out come in patients with a recent myocardial infarction

3 Corticosteroids were only given to treat shock or the SK-induced allergic reaction. It is not mentioned whether steroids were given more often in the heparin than in the SK treated group

4 The general treatment was not standardized

5 Since the authors wanted to give the SK treatment early it was not possible to wait until the enzyme and ECG data were available. Thus, some patients may have been withdrawn from the final evaluation for each group of patients because of uncertain diagnosis.

6 Data on changes in the blood fibrinolytic and coagulation systems are not presented it is therefore difficult to judge at what level the patients were treated

Poliwoda (1966) and Poliwoda Diederick Schneider Rodenburg Heckner Körtge Van de Loo Pezold Praetorius, Schmutzler and Zekorn (1966) reported the results of ECG evaluation of the same joint trial. ECG tracings from 234 patients were analysed 134 SK treated and 100 heparin treated In the SK treated patients, they found a more rapid development of evidence of infarction in the ECG and an earlier reversal (e g. ST-elevation). It was noted that the accelerated tendency towards a normal ECG pattern in the streptokinase group was seen in the first days only

1 The remarks made above concerning the report of Schmutzler Heckner Körtge Van de Loo Pezold Poliwoda Praetorius and Zekorn (1966) apply here also especially the lack of strict randomisation.

2 Although it is taken for granted that a rapid trend toward normalisation of the ECG changes is a favourable prognostic sign it would have been particularly interesting to know if the mortality rate was different between patients with rapid evolution and those with slower evolution of the ECG signs.

Praetorius and Körtge (1966) Praetorius Schneider Heckner Van de Loo and Pezold (1967) presented the data of the serum enzyme studies performed on patients from the same trial They studied the evolution of transaminase (SGOT) and creatine phosphokinase (CPK) in samples drawn form 94 SK treated and 24 heparin treated patients. Because of the small number of patients in the heparin treated group for which serum enzymes were available the authors did not analyse the heparin treated group They divided the SK treated patients into two subgroups sub-

group A 54 patients treated within the first three hours and subgroup B 40 patients treated between 4 and 12 hours. A mathematically constructed curve was obtained in both subgroups for CPK and SGOT In the late phase of these curves no difference was found between subgroups A and B In either the serum GOT or in the CPK curve In the early phase of the CPK curve and of the serum GOT values, there was a tendency to increase more rapidly in subgroup A than in the subgroup B

Thus, for the samples drawn 4 hours after the onset of symptoms there was a significantly higher ($0\ 02 > p > 0\ 01$) serum CPK level in group A than in group B No significant difference was found between subgroups A and B in the maximum level reached for the serum GOT or serum CPK.

The following comments can be made

1 The validity of the control group is open to discussion such a control group could only show whether a difference in enzyme evolution is produced by early or late SK eatment however a valid conclusion uld be drawn only if patients were andomly allocated to early or late treatment In fact the allocation to one or other group was in this study not decided by the investigator but by other events.

2 As mentioned in the discussion of their paper one should not transpose the differences between early and late SK treated groups to differences between heparin and SK treated groups.

Remy and Gebauer (1966) have treated 55 patients with recent (less than 4 hours) myocardial infarction with streptokinase. The initial dose was 250 000 units SK and further treatment was adjusted according to SK resistance and thrombin time The authors indicated that it was possible in the course of the study to reach a more standardized infusion scheme In fact all patients (n = 55) with a recent myocardial infarction and without contra-indications were treated with SK and compared to a control group (n = 120) the latter was composed of these patients admitted to hospital during the same period but with an older myocardial infarction and this group was treated with heparin. The mortality was lower in the SK (18 2 %) compared to the heparin (30 0 %) treated group The authors feel that there was also a reduction in the frequency of heart failure (16 4 % in SK and 23.3 % in the control group) and embolic complications. The ECG evolution was more rapid

The following comments can be made

1 The selection criteria of the experimental (SK) and control group (heparin) were different and no randomisation was achieved

2 Comparability of the two treatment groups was not demonstrated

3 The authors do not show which changes in the blood fibrinolytic and coagulation systems were produced

Hiemeyer Rasche and Diehl (1969) have reported on 42 patients with recent myocardial infarction (less than 12 hours) Those admitted during the first three months of the year under investigation (1967) were treated with heparin the other patients admitted in 1967 received SK The mortality within the first month after the infarct (excluding the first 24 hours) of these two groups was compared to the mortality of a third group of similar patients admitted during the previous year (1966) but treated with neither SK nor heparin. A significant reduction in mortality was found in the heparin – SK group (21 5 %) treated in 1967 compared to the group treated without heparin nor SK (41 7 %) in 1966

It can further be calculated from the figures given by the authors that the

mortality was lower in the SK treated group (5/28) compared to the heparin treated group (4/14) using the chi two tailed square test, we did not find the latter difference to be significant ($p > 0.1$)

The following comments can be made

1 No randomisation between the heparin-SK and the other group was planned In fact only from January 1967 the University of Ulm was in charge of the patients. It was not stated if this led to other changes in the care of coronary patients the general therapy was not specified

2 The reasons for exclusion of a patient from the study are not mentioned

3 Patients who died within the first hours were excluded

4 *Heparin and SK were administered using* a standard dosage scheme biochemical changes produced by this therapy were not reported

Let us now discuss the trial reported in this paper

1 No stratification was introduced and it is therefore possible that differences which could exist in certain subgroups were lost in the total evaluation Since the patients were not stratified before the start of the study subdivision should be considered as a procedure not beyond criticism. The second *and third* analysis of the data presented here were only made in an attempt to find subgroups and criteria, which could be used for the stratification and organisation of further clinical trials on this subject

2 Furthermore, some charts did not contain all data and it could not be confirmed that the patients in whom the ECG tracings, and results of coagulation and fibrinolysis studies were available constitute a sample representative of the total population of patients studied

3 The results of the CTT determinations were not analysed since it was suspected that delay in the performance of this test *after blood sampling often resulted in low* values

4 The amount of heparin to be infused was fixed at a rather low rate this was the result of a compromise between those *investigators who believe that heparin is* of definite advantage in the early treatment of recent myocardial infarction, those who think it is useless and those who believe it could be harmful In fact the thrombin times were only slightly prolonged in most of the cases, as described above yet bleeding complications occurred during this infusion period From this study we can only draw conclusions about the comparative value of the here applied method of heparin and SK treatment

5 The minimum criteria for infarction were not defined and a diagnosis of infarction was made by the cardiology staff of each collaborating centre We tried to eliminate this drawback by asking an expert outside of the study to review the ECG tracings on a double blind basis.

6 The allocation of patients into subgroups was done using a closed envelope system. *However none of the check systems* described above were used to make sure that each patient was indeed allocated to the group for which he was scheduled

7 Experience obtained in a previous unpublished study has shown that clearly defined and standardised general treatment was considered not feasible. Therefore in present study each centre applied its own standing rules for general treatment in both the heparin and the SK group

8 *The follow-up* was restricted to the hospitalisation period, which may have been different in both groups.

Although no significant difference in outcome was obtained in the present study

this does not exclude the possibility that a favorable result could be reached by SK administered using another dosage scheme in more selected subgroups. Therefore a new trial has been organised and is now running in different European centres.

SUMMARY

Patients diagnosed in different centres as having, according to the criteria of each centre, a recent (of less than 72 hours duration) myocardial infarction were preselected for the present study after exclusion of those patients where heparin or streptokinase treatment was considered contra-indicated (negative criteria) In each centre all patients received the standard general treatment for recent myocardial infarction, proper to each centre.

Using a sealed envelope system the candidates for the study were allocated at random in a heparin and streptokinase group The patients of the heparin group received an initial dose of 100 mg heparin over a 30 minutes period and thereafter 12.5 mg per hour during 72 hours. The patients belonging to the streptokinase group received an initial dose of 1 250 000 units streptokinase within 30 minutes and during the next 72 hours 104 000 units streptokinase per hour Twenty five mg prednisolone was injected intravenously to all patients just before the initial dose of heparin or streptokinase and daily during the first three days.

In 167 patients from 8 different centres, the randomisation was considered valid to allow a first analysis 84 patients were treated with heparin and 83 with streptokinase. On retrospective analysis these two groups were found to be comparable as no significant difference was found at the time of admission into the study in the effect of several parameters which might influence the course of a myocardial infarction

During the infusion period the erythrocyte sedimentation rate increased in the heparin treated group but decreased in the streptokinase group Death bleeding complications, rigor rash and shock were not observed more frequently in one of the groups.

No significant difference could be found between these two groups as a whole in the hospital mortality and S G O transaminase at different intervals after the start of infusion.

On completion of the trial patients of both groups were divided in subgroups, according to several parameters for example the interval between the onset of the acute retrostenal pain and the start of the heparin respectively streptokinase infusion presence of definite electrocardiographic signs of myocardial infarction. No significant difference in hospital mortality was found between streptokinase and similar heparin treated subgroups

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A clinical and biochemical study
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LONG-TERM TOLBUTAMIDE TREATMENT AFTER MYOCARDIAL INFARCTION

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A clinical and biochemical study of 178 patients without overt diabetes

By

JUHANI PAASIKIVI

STOCKHOLM 1970

Tryckeri Balder AB, Stockholm 1970

PREFACE

This investigation was primarily made possible by the support of Professor Gunnar Biörck, M.D Head of the Department of Medicine, Karolinska Institutet at Serafimerlasarettet who also provided the many facilities necessary for its progress and fulfillment.

The association between glucose metabolism and atherosclerotic vascular disease has been subject to an ever increasing amount of research. In 1963 the results already arrived at by Fredrik Wahlberg, M.D prompted the start of a trial of antidiabetic treatment in patients recovering from a myocardial infarction.

Together with Fredrik Wahlberg M.D Mrs Gertrud Degerstedt has taken a very active part in my work throughout the study. Their friendship and encouragement have been essential.

My appreciation is due to Bengt Thomasson, M.D for his generous help with the revision of the manuscript including language corrections together with Michael Shirley M.D

My thanks are also due to Olof Edhag, M. D Erik Orinius, M.D and Andreas Sjögren, M.D for their valuable advice and criticism. Torbjörn Lundman, M.D introduced me to computer technique.

Professor Lars A. Carlson, M.D enabled the lipid analysis and also offered positive criticism.

I also wish to thank Mrs Ingrid Braunstein, Miss Lisbeth Gyllenstierna, Mrs Gunilla Haag, Mrs Kim Hellman, Mrs Viveca Hultén, Miss Rhode Jansson and other co-worker at the Department of Medicine for their contribution to the fulfillment of this investigation.

The study was supported by grants from the Swedish National Association against Heart and Chest Diseases, and Karolinska Institutet for computer analysis.

The tolbutamide and placebo tablets have been provided by Messr Svenska Hoechst AB

Last but not least I wish to express my gratitude to all patients who took part in the investigation.

CONTENTS

k value diabetic } abnormal borderline } normal	17
k_o value (k value of the initial IVGTT)	20
IVGT (intravenous glucose tolerance) IVGTT (intravenous glucose tolerance test)	16
SGOT (serum aspartate aminotransferase) SGPT (serum alanine aminotransferase) LHD (serum lactic dehydrogenase)	11
A V block II—III (atrioventricular block II and total block) Cardiac complications Major arrhythmias SVEB (supraventricular ectopic beats) VEB (ventricular ectopic beats)	15
ESR (erythrocyte sedimentation rate) WBC (white blood cell count) BSA (body surface area)	16
N.S (statistically not significant)	17
Risk ratio	49
CHD (coronary heart disease) CVD (cardiovascular disease) OGT (oral glucose tolerance) OGTT (oral glucose tolerance test)	

Tolbutamide (1-butyl 3(p-tolyl)sulfonylurea) belongs to the sulfonylurea group and introduced in 1955 as oral antidiabetic agent after long and significant research work Loubatières and his collaborators Extensive reviews of tolbutamide has been published by Creutzfeldt & Söling (1961) and Tucker (1965)

Tolbutamide is used in the mild adult maturity onset non ketotic type of diabetes mellitus Its mode of action is still not wholly established but convincing evidence suggest it to be that of stimulation of synthesis and release of endogenous insulin from the pancreas The plasma half life is 3—8 hours Its toxicity has been established to be of low magnitude but owing to interaction its hypoglycemic effect may be potentiated by sulphaphenazole (Korsgaard Christensen et al 1963) or dicoumarol (Kristensen & Molholm Hansen 196)

Coronary heart disease has been the main object of many clinical studies of atherosclerotic vascular disease. Epidemiological studies have also shown the increased risk of developing coronary heart disease in the presence of diabetes mellitus, hypertension, and hyperlipemia as well as the role of environmental and habitual factors (Biörck et al. 1956, Dawber et al 1962, Keys et al 1963 Epstein 1967 a) The incidence of coronary heart disease has been reported to be greater not only in subjects with overt diabetes mellitus but also in those with impaired glucose tolerance only (Ostrander et al. 1965 Epstein 1967 b) thus corroborating previous findings of a higher frequency of impaired glucose metabolism in patients with coronary heart disease, (see survey by Wahlberg 1966)

Investigations of the intravenous glucose tolerance in survivors from myocardial infarction at Serafimerlasarettet have shown that in about 60 per cent of them this was abnormal, i.e. 4 times the rate found in controls all patients with overt diabetes having been excluded before the tests (Wahlberg 1966)

When the present study started it was already known that prolonged tolbutamide treatment could normalize glucose tolerance in asymptomatic diabetics (Fajans & Conn 1962) but nothing was known about the prognostic value of this achievement. Moreover the general assumption that the *development of cardiovascular changes is retarded* by treatment in patients with mild, non-ketotic diabetes had not been undisputably reported (Knowles 1964, as quoted by Ricketts 1965) It was thought that the study would also give some information about the effect and value of early treatment of asymptomatic diabetics in general.

The long term prognosis of diabetic survivors from myocardial infarction was found less favourable than that of non-diabetic survivors by Biörck et al. (1958) Sievers (1963) Partamian & Bradley (1965) This difference was not observed by Weinblatt et al. (1968) However it has been shown that abnormal glucose tolerance in patients without overt diabetes implies unfavourable long term survival after a first acute myocardial infarction (Wahlberg 1966) as it does in patients with intermittent claudication (Kingsbury 1966)

The different mechanisms considered to lead to myocardial infarction and the statistical association of a number of factors with coronary heart disease initiated numerous studies of long-term therapeutic trials in survivors from myocardial infarction. The results of such investigations with pharmacological agents such as anticoagulants or oestrogens have been conflicting, and the same is true of dietary management. At best, the long-term prognosis appeared to be slightly improved.

By 1962 tolbutamide had been reported to have favourable effect on ischemic cardiovascular disease in patients with as well as without overt diabetes (Singh & Bardhan 1959 Fabrykant & Ashe 1960 Pearnley et al. 1960 Singh et al. 1962) although no effect had also been reported (Clarke & Naylor 1961) No study in patients recovering after myocardial infarction had so far been published

THE AIM OF THE STUDY

The finding of a high rate of impaired glucose tolerance in patients with coronary heart disease and its prognostic implication prompted a study of antidiabetic treatment in survivors from a myocardial infarction. Consecutive survivors from a first myocardial infarction were therefore subse-

quently treated either with tolbutamide or a placebo

The influence of prolonged tolbutamide treatment on a number of factors influencing the long term prognosis after an acute myocardial infarction has been investigated including its effect on intravenous glucose tolerance in those subjects without overt diabetes

The patients of the present study were 178 survivors from a first myocardial infarction, for which they had been admitted acutely and treated at the Department of Medicine at Serafimerlasarettet, Stockholm, from January 1963 through July 1967. During this time a total of 270 survivors from a first myocardial infarction were discharged from the Department of Medicine, but 92 had to be excluded for reasons given below. The follow-up was terminated July 31st, 1968, which gave a minimum observation time of one year per patient.

Criteria for selection were absence of the following conditions: History or signs of overt diabetes mellitus or other disease known to interfere with carbohydrate metabolism, malignant neoplastic disease, and rheumatic or other heart disease not considered to be of coronary origin.

DIAGNOSIS OF MYOCARDIAL INFARCTION

This diagnosis was based upon the coexistence of at least 2 of the following 3 criteria: a typical history, serum enzyme (SGOT, SGPT, LDH) pattern, and ECG findings suggestive of acute myocardial infarction according to the standards set by the Department of Clinical Physiology at Serafimerlasarettet.

A history of acute myocardial infarction was considered positive if the patients had experienced central chest pain for at least 30 minutes.

Serum enzymes, i.e. aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and lactic dehydrogenase (LDH) were determined according to a modification by Messrs AB Kabi of the methods of Wróblewski & LaDue (1955 a, 1955 b). The normal values of these enzymes at the Department of Clinical Chemistry at Serafimerlasarettet have remained essentially unchanged during the time of the study. Values exceeding 40 Units/ml have been considered pathological.

Electrocardiographic evidence of an acute myocardial infarction was considered present if in at least 3 electrocardiograms there occurred a Q-wave and/or ST T-changes indicating myocardial infarction in at least 2 leads mainly according to the criteria of the Minnesota code (Blackburn et al. 1960); other ECG-changes were disregarded.

The electrocardiograms were recorded with a 4 channel direct writing ink jet electrocardiograph (Mingograph 42, Elema Co). The leads used were I, II, III, aVR, aVL, aVF, CR1, 2, 4, 5, 7, V 1, 2, 4, 5, 7.

Electrocardiograms were recorded daily during the first 3 days of hospitalization, thereafter routinely once a week or more often when indicated.

COMMENTS

The exclusion of an earlier myocardial infarction was based upon the absence of a history of myocardial infarction or of severe heart attack treated for more than 3 days in hospital or at home. Patients with electrocardiographic evidence of previous myocardial infarction or other heart muscle damage were not accepted.

In defining a first myocardial infarction in this way it is possible that a number of patients with reinfarctions might be included as was definitely shown in autopsy studies of patients dying from their first clinically diagnosed myocardial infarction. As evidence of an old infarct has been found at autopsy in 34 to 50 per cent in the above mentioned category of patients (Sievers 1963, Westlund & Hougen 1964, Master & Geller 1969) similar rates might also occur in a series of survivors. Such silent myocardial infarctions can be assumed to have been distributed randomly in the patients studied and are therefore thought not to influence the results.

TABLE 1 Diagnostic criteria of myocardial infarction

					No. of patients	Per cent
Pain	+		+	+	173	97
ECG	+	+	+		164	92
Enzymes	+	+		+	17	97
No. of patients	153	5	6	14	178	100
Per cent	86	3	3	8		

As listed in Table 1 all 3 diagnostic criteria for myocardial infarction were fulfilled in 86 per cent of the cases. In 3 per cent the diagnosis was based upon laboratory findings only and in the remaining 11 per cent a history of chest pain constituted one criterion together with a positive laboratory finding.

REASONS FOR EXCLUSION

As mentioned above, 92 out of 270 survivors from a first myocardial infarction treated at the Department of Medicine at Serafimerlasarettet had to be excluded from the present study. The reasons are summarized in Table 2. Forty-two would have participated in the control group and 50 in the tolbutamide group.

Overt diabetes mellitus was considered present if a patient repeatedly had glucosuria and a fasting blood glucose exceeding 110 mg per 100 ml under basal conditions. Previous treatment of diabetes, even if temporary, was sufficient cause for exclusion. Twenty-one patients were excluded because of overt diabetes, i.e. 8 per cent of the 270 patients with a first myocardial infarction, an incidence which is in accordance with those of other studies (Sievers 1963, Wahlberg 1966).

Other diseases known to affect glucose tolerance led to the exclusion of 5 patients, 3 with a history of thyroid dysfunction and 2 with severe renal disease. Eleven patients with neoplastic malignant diseases, surgically treated or not, were also excluded because of possible non-coronary influence on prognosis, as were 3 patients with rheumatic valvular heart disease.

Other reasons for exclusion. Six individuals were not asked to participate because of inadequate cooperation due to cerebral impairment or vagrancy and alcoholism.

Refusal to take part in the study decreased the number of participants by 24. The reasons was, in the majority of the cases, that the patients wished to continue visiting their regular physicians after discharge from the hospital. No efforts were made to persuade these patients. Three patients expressed reluctance to be treated with an unknown drug and therefore would not participate.

Finally 6 patients were *erroneously* omitted, mainly because no one responsible for the trial was available at the time of their discharge from hospital.

TABLE 2 Survivors from a first myocardial infarction at the Department of Medicine at Serafimerlasarettet from January 1963 through July 1967

	Number of subjects		
	Male	Female	Total
All survivors	195	75	270
Reasons for exclusion from the study			
Overt diabetes mellitus	13	8	1
Metabolic diseases		3	5
Malignant neoplastic diseases	4	7	11
Rheumatic valvular heart diseases	0	3	3
Cerebral impairment and/or inability to cooperate	0	4	4
Vagrancy or alcoholism		0	
Refusal to participate	14	10	4
Erroneously omitted	2	4	6
Not living in Stockholm area	13	3	16
Included in the study	143	35	178

TABLE 3 *The mean age and sex ratio of patients surviving an acute myocardial infarction in some Scandinavian materials*

	Sievers 1963	Mosbech & Dreyer 1966[b]	Serafimerlasarettet 1950—59[c]	Serafimerlasarettet 1958—62[a]	Serafimerlasarettet 1963—67[a]	Study group[a]
Male	58	63	60	60	58	58
Female	66	67	66	67	68	66
Total	61	64	63	62	61	59
Sex ratio male/female	2.0	3.6	2.5	2.9	2.6	4.4

) First myocardial infarction only
) Reinfarctions included
) Reinfarctions included (Wahlberg 1963)

AGE AND SEX

As shown in Table 3 the mean age of all 270 cases from 1963 through July 1967 was 61 years, 58 for the males and 68 for the females. The sex ratio was 2.6 men to one woman.

One hundred and seventy-eight patients remained after exclusion of 50 men and 42 women from the total group. The mean age of the study group was 59 years, 58 years (range 37—81) and 68 years (range 51—80) for the males and females, respectively. The sex ratio was 4.4 which differed from that of the primary group ($P < 0.05$).

COMMENTS

Relatively more women than men were excluded as higher age, concomitant malignant disease or mental impairment was more common among women. They were also more often under the care of another physician when suffering the myocardial infarction which led to their refusal to take part in the trial.

The sex distribution among the excluded subjects also influenced the mean age of the study group which was therefore significantly lowered by 2 years ($P < 0.001$).

To evaluate the composition of the study group and the effect of the exclusions discussed above a comparison was made with other and larger Scandinavian studies of myocardial infarction as well as earlier patient samples at Serafimerlasarettet.

The mean age of 1584 four week survivors from a first myocardial infarction during 1935 through 1959 in the total population of Malmö was not given by Sievers (1963) but can be estimated from his figures to have been 61 years, 58 years for the men and 66 years for women. The sex ratio was 2.0.

The mean ages of all 646 myocardial infarctions hospitalized and discharged alive in Denmark during the months of March and April 1963 as reported by Mosbech & Dreyer (1966) were 63 years for the men and 67 years for the women. The reinfarctions, comprising approximately 20 per cent, were included. The sex ratio was 3.6.

The mean age of 446 survivors from an acute myocardial infarction treated at Serafimerlasarettet during 1950—59 was 62 years, 60 for men and 66 for women (Wahlberg 1963). The reinfarctions were, however, not excluded. The sex ratio is not given but can be calculated to have been 2.5 men to one woman.

The mean ages and sex ratios of 171 short-term survivors from a first myocardial infarction treated at Serafimerlasarettet from 1958 through 1962 as well as those from 1963 through July 1967 are also entered in Table 3.

The mean age of all survivors from myocardial infarction at Serafimerlasarettet throughout the sampling time differed maximally by 3 years from the Scandinavian studies cited. This difference is 0—3 years for the men and 0—2 years for the

women. The difference is greatest in comparison with the Danish series, the mean age of which presumably was increased by the inclusion of patients with reinfarction. The sex ratios are similar in all the infarction series. It is probable that a selection according to the principles in this study would result in corresponding changes of composition, and therefore the present study group in its way is thought to be representative of survivors from a first myocardial infarction.

II

METHODS

DEFINITIONS

A hereditary tendency for myocardial infarction or diabetes was considered to be present if the patient was aware of either disease among his parents, siblings or children.

Cardiac functional capacity was classified in 4 classes according to the New York Heart Association (1964).

Ordinary physical activity denotes the usual level of the patient's physical activity during the decade prior to the infarction. The subjects were grouped into one of 3 categories: a low degree of physical activity, moderately strenuous physical activities, and strenuous physical activities. The subject's occupational activity mainly determined the grouping but in some patients the physical activity in their spare time in the 2 first groups indicated a classification in the next higher group.

Smoking and drinking refer to the dominant habit during the decade preceding the myocardial infarction. A person smoking usually no more than 15 cigarettes daily or the equivalent in pipe or cigars was classified as a light smoker, others as heavy smokers. Alcohol consumption was considered as casual if not claimed to be daily, otherwise regular.

Angina pectoris was defined as central chest pain with or without radiation, reproducible and occurring with effort or emotional strain exceeding 5 minutes and relieved by rest or nitrites.

Intermittent claudication was considered to be present when pain in the calves was provoked by walking or hurrying, forcing the subject to stop or slacken pace and disappearing only at rest, but never while walking continued (Rose 1962).

Hypertension was considered present when a diastolic pressure of 100 mm Hg or more had been recorded on repeated occasions during hospitalization and subsequently or if the patient previously had been treated with antihypertensive drug.

Previous congestive heart failure was considered to have occurred in patients who had had undue dyspnoea or who had been continuously treated with digitalis.

Shock or pulmonary edema were considered to have been present if mentioned in the case records.

Cardiac complications during the hospital stay refer to electrocardiographical evidence of any of the arrhythmias or blocks mentioned below or the occurence of shock, pulmonary edema, pericarditis or suspected extension of the myocardial infarction.

Obesity was defined as 10 per cent overweight or more according to the height and weight tables published by the Danish Insurance company Hafnia (Kramp 1956).

Fatal myocardial reinfarction in the absence of autopsy was considered to have occurred if the reinfarction had been diagnosed in hospital or if death had been sudden.

LABORATORY TESTS

Electrocardiograms (ECG). The electrocardiographic diagnosis of atrioventricular block II—III (A V block II—III), atrial fibrillation or flutter, supraventricular or ventricular ectopic beats (SVEB or VEB) or ventricular tachyarrhythmias were made according to the standards of the Department of Clinical Physiology.

The occurrence of atrial fibrillation, bundle branch block or A V block II—III or ventricular tachycardia or fibrillation was denominated as "major arrhythmias". For technical reasons this was a modification of the criteria set by Stock et al (1967) and Denborough et al (1968).

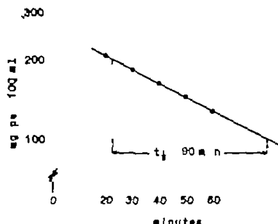


Fig 1 Calculation of the k value.

Electrocardiographic exercise test This test was performed on a bicycle ergometer* according to the principles of the Department of Clinical Physiology (Sjöstrand 1960) The routine working time was 18 minutes continuously with 6 minutes on each load of 300 600 and 900 kgf m/min The test was terminated if angina pectoris, severe dyspnoea or fatigue developed, or as in a few instances, when any alarming change was seen on the ECG The total work was expressed as the sum of the loads in kgf m/min. for each minute. The pulse rate at steady state was defined as that registered during the fifth or the last minute of a period.

The heart volumes was estimated with the patients in the standing position (Liljestrand et al. 1939) and relative heart volume expressed in ml/m² body surface area (BSA) according to Jonsell (1939) as a part of the routine program of the Department of Roentgenology at Serafimerlasarettet. Heart volumes exceeding 500 in men and 450 ml/m² BSA in women were considered abnormal In case of repeated examinations the one in connection with discharge from hospital was noted for the study

Erythrocyte sedimentation rate (ESR) was measured in the wards, *white blood cell count* (WBC) and the serum enzyme determinations were performed by the Department of Clinical Chemistry

Blood glucose was determined enzymatically according to Marks (1959) from capillary blood samples from the earlobes. The linear function of glucose concentration and photometric extinction within the range 0 to 400 mg pr 100 ml was tested at least twice annually The blood sampling and the determination of glucose values were carried out by a specially assigned technician.

The intravenous glucose tolerance tests (IVGTTs) were performed after an overnight fast and an ordinary carbohydrate intake during 2—3 days preceding the test. The adherence to given instructions was routinely checked. All medicine was withheld on the morning of the test (tolbutamide for 60 hours) The patient was recumbent during the test, which was preceded by 15 minutes rest. After duplicate sampling of fasting capillary blood, 25 g of glucose in 50 per cent aqueous solution were injected intravenously in 2—4 minutes, zero time being set 2 minutes after the start of the injection. From the zero time capillary blood samples were taken every 10 minutes for one hour the samples at 20 40 and 60 minutes being duplicated The blood glucose values were plotted on a semilogarithmic graph, the logarithms of absolute blood glucose values between 20 and 60 minutes forming a straight line when plotted against time as originally suggested by Hamilton & Stein (1942) Blood glucose values lower than 100 mg per 100 ml or not exceeding the fasting blood glucose value by 10 mg per 100 ml were disregarded (Wahlberg 1966) The half life of blood glucose in minutes ($t_{½}$) was determined graphically by extrapolation and the glucose utilization was expressed as a *k-value* representing the disappearance of blood glucose in per cent per minute as shown in Fig 1

The following formula was used for the calculation of the k value $k = \frac{0.693 \cdot 100}{t_{½}}$

For practical reasons semilogarithmic graphpaper was used, on which the absolute blood glucose values were plotted, as illustrated by Fig 1

*) Monark-Crescentbolagen AB Stockholm

*) Equivalent to *kil pond meter/m* (kp m/min)

The test has been thoroughly discussed by Ikkos & Luft (1957) and Wahlberg (1966) The same classification as in the latter report was used in the present study i e.

Diabetic IVGT	k value	≤0 90
Borderline		0 91—1 10
Normal		≥1 11

Serum cholesterol and triglycerides Before the IVGTT was performed blood was withdrawn for lipid analysis. This was allowed to clot at room temperature for one hour and the serum was then separated by centrifugation. The sera were stored at —14 C until analyzed. Serum cholesterol was determined essentially according to Sperry & Webb (1950) and triglycerides according to Carlson (1963)

STATISTICAL METHODS

Statistical analysis was as a rule performed with the chi-square test (with Yate s correction factor when indicated by small samples) Wilcoxon s rank tests for paired and unpaired samples or if normal distribution was considered probable, Student s *t*-test and regression analysis were used (Documenta Geigy Scientific Tables 1962)

The cumulative survival rates were estimated by using the life table method (Cutler & Ederer 1958)

Probability levels lower than 5 per cent were considered to indicate statistically significant differences.

COMMENTS

CLINICAL METHODS

The definitions of cardiovascular symptoms used this study were arbitrarily chosen but do not differ considerably from those generally met with in similar clinical investigations The same was valid for the grouping of the patients as regards their physical activity smoking and drinking habits. As the purpose was not to find out the true incidence of these parameters in an infarction population—this had already been done in larger and less selected patient groups (e g. Sievers 1963 Kannel et al. 1961 Kannel 1966)—but to acquire some information about their relationship to IVGT the classification used seemed sufficient. In spite of possible sources of errors, the information given by the patients was accepted as it was considered that inherent errors would be evenly distributed in the 3 IVGT groups to be investigated. The patients IVGT was usually not known at the time of the interview

LABORATORY METHODS

The ECGs were routinely interpreted by the staff of physicians of the Department of Clinical Physiology whose members were unaware of the selection of patients for the study

THE GLUCOSE TOLERANCE TEST

There were 2 main reasons for choosing the intravenous method when testing the glucose tolerance. By 1963 only 2 studies of oral glucose tolerance had been published in connection with acute myocardial infarction and their results did not agree (Goldberger et al. 1945 Sowton 1962) Considerable differences of opinion existed—and exist—as to performance and interpretation of oral glucose tolerance tests At Serafimerlasarettet the IVGTT had been used since 1960 in this context and found to have a good reproducibility within intervals of days and years in patients who had recovered from acute myocardial infarction. Therefore this test seemed most apt for the present study it is simple and takes a short time to perform. Thrombophlebitis was a rare sequela, occurring in less than one per cent, i.e. after 3 out of 386 tests. The result of the IVGTT was easy to express and con enient for statistical analysis.

The k values given in the present study were determined graphically throughout. When recently an electronic desk calculator, (Hewlett Packard) became available at Serafimerlasarettet, the reliability of these determinations was compared with k values calculated mathematically from the linear coefficients of the corresponding blood sugar values (using the method of least squares of the

TABLE 4 Comparison of 2 methods of determining the k value

	k value		k-difference		Technical error
	Mean	S.D.	Mean	S.D.	
Graphical	1.170	0.003	0.020	0.0 1	0.020
Mathematical	1.113	0.003			

logarithms). The k values of 50 randomly selected IVGTTs were determined graphically and mathematically. Using the formula $\sqrt{\frac{d^2}{2n}}$ in which d denotes the difference between the 2 k values of each slope, the results of this comparison are presented in Table 4. No statistically significant differences emerged, and in no instance did any change in IVGT grouping occur.

PROCEDURE

When a patient fulfilled the criteria for participation in the study he was informed before discharge from hospital about the special ambulatory supervision at the outpatient clinic for post infarction patients. He was further told that a new drug, aiming to influence carbohydrate metabolism and prognosis in a favourable way, would be tried. The existence of a placebo was not mentioned.

Nobody was persuaded to take part.

PRINCIPLES FOR TREATMENT

During hospitalization all patients were given routine treatment by the responsible staff. If anticoagulants had been used these drugs were discontinued at the start of the study.

The treatment of cardiovascular diseases or complications during hospitalization and subsequently, i.e. heart failure, arrhythmias, angina pectoris or hypertension has been uniform and according to generally accepted principles based primarily on digitalis, diuretics, quinidine, procainamide, nitrites or hydralazine.

Low caloric and low fat intake was recommended and obese patients were urged to reduce weight. Otherwise no dietary recommendations were given.

SELECTION OF PATIENTS FOR TOLBUTAMIDE AND PLACEBO TREATMENT

Even or odd birth date determined whether the patient received a placebo or tolbutamide.

DOSAGE OF TOLBUTAMIDE AND PLACEBO

Tolbutamide or placebo tablets were stored in bottles of identical appearance but for a small detail on the label that enabled a distinction to be made between the contents.

At discharge from hospital the initial prescription was half a tablet twice daily for a month, to be followed by half a tablet 3 times a day and after another month the maximal dosage of 2 tablets per day but in each instance only if during the interval no symptoms suggesting hypoglycemia had occurred. Hence, the maximal dosage of tolbutamide was one gram in 2 doses daily.

All patients were made aware of possible hypoglycemic symptoms during the treatment, and at the clinic visits during the follow-up they were routinely asked about symptoms such as undue hunger, sweating, dizziness, palpitations, increased angina pectoris or decompensation.

CONTROL AND FOLLOW-UP

The patients were seen routinely once a month during the first 3 months after discharge from hospital, and from then on every third month. This schedule was of course abandoned, if complications or other circumstances necessitated more frequent visits. The examinations took place in the outpatient clinic and were performed by one of the 2 doctors responsible for the study. Each visit included history taking, an approximate classification of physical capacity and physical examination including blood pressure recording and weighing.

The laboratory tests were performed either at these visits or at other convenient times as presented earlier in this Chapter and later in Chapters VI and VII

COMMENTS

THE STUDY

Before 1963 treatment with tolbutamide had been reported in diseases such as paralysis agitans, multiple sclerosis, acne and atherosclerotic disease in non-diabetic patients (Singh & Bardhan 1959 Cohen & Cohen 1959 Gates & Hyman 1960 Foster et al. 1961 Clarke & Naylor 1961 Singh et al. 1962) in most cases without serious side-effects. Severe hypoglycemias in these patient categories had been seen, however (Schwartz 1961 Yonet & Ballard 1961) even with fatal outcome in one case (Kreeger 1962) Tolbutamide treatment in recommended doses had also been reported to result in fatal hypoglycemia in patients with overt diabetes (McKendry 1957) A double-blind administration of tolbutamide to patients without overt diabetes was therefore considered hazardous, and it was thought mandatory to be able to ascertain whether a patient was receiving tolbutamide or a placebo in an emergency situation. To reduce the risk of bias all participants were uniformly informed about symptoms of hypoglycemia and extreme care was taken to avoid possible misunderstandings in the instructions, general care and treatment given to the patients.

A dosage of one gram tolbutamide, being common in treatment of overt diabetics, was chosen as the maximal dose in the present trial.

The choice of birth date as a means of allocating the participants to treatment groups seemed simple, definite and fulfilling all conditions for randomization in a controlled trial when a double-blind method could not be used The number of patients the tolbutamide-treated group exceeded that of the control group (ratio 1 14) but this difference was not greater than that which could have been excepted to occur by chanse ($P>0.05$)

During the initial period of the trial nothing was of course known about any possible benefit of tolbutamide. At discharge from hospital all participants were informed about the background of this new form of treatment i.e. the possible important role not only of lipids but also of carbohydrate metabolism in the progress of their disease. They were told that with the treatment offered—tablets as well as continuous instructions about diet and physical exercise—it was hoped to influence the course of their disease favourably It was not felt necessary to reveal the blind test nature of the treatment as no one was omitted from any generally accepted therapy

Long-term anticoagulant therapy after a myocardial infarction was generally practised in the 1950ies. But in 1962 the opinion about this treatment was more divided owing to conflicting results of controlled studies (e.g. McMichael & Parry 1960 or editorial in The Lancet 1962) For this reason it was not felt that the patients were deprived of a treatment generally accepted as essential when anticoagulant therapy was terminated at discharge from hospital.

Routinely most of the patients discharged from Serafimerlasarettet after a myocardial infarction were assigned to the ordinary outpatient clinic for subsequent control. It was therefore usually considered as a favourable offer to the participants to be supervised at a special clinic free of charge by the same 2 physicians who had full knowledge of their case history and whom they could call upon case of emergency

Concluding a double-blind trial with tolbutamide in non-diabetics was considered hazardous. Necessary precautions were taken to randomize the patients to establish a controlled long-term trial of the effect of antidiabetic treatment on the survival after a first myocardial infarction.

CLINICAL CHARACTERISTICS OF THE ACUTE MYOCARDIAL INFARCTION IN RELATION TO IVGT

INTRODUCTION

Overt diabetes mellitus has repeatedly been pointed out as an aggravating condition in connection with myocardial infarction. Shock and congestive heart failure, which in themselves influence the immediate outcome in acute myocardial infarction unfavourably have been reported also to occur more often in diabetics than in non-diabetics (White et al. 1960 Partamian & Bradley 1965) and Sievers (1963) found an increased acute mortality also in diabetic patients with uncomplicated myocardial infarction. On the other hand, conflicting results were obtained by Cole et al. (1954) and Weinblatt et al (1968) As to long-term prognosis after myocardial infarction this has been reported to be worse in diabetics than in non-diabetics by some authors but not by others (Biörck et al. 1958, Sievers 1963 Partamian & Bradley 1965 Cole et al. 1954, Weinblatt et al. 1968)

The occurrence of transitory hyperglycemia and glucosuria in non-diabetic patients during the first days after myocardial infarction was observed by Levine & Brown in 1929 a finding subsequently verified by others (Edelmann 1934, Raab & Rabinowitz 1936) Its cause might be a suppression of insulin release (Allison et al. 1969) and it seems to be associated with the severity of the infarction and the short-term mortality (Eckerström 1951 Forssman 1954, Sievers 1963) Hyperglycemia during the first days after myocardial infarction does not necessarily indicate permanently impaired glucose tolerance (Sowton 1962, Wahlberg 1966, Datey & Nanda 1967) even if such findings have been reported by Frehner & Wegmann (1963) The long-term prognosis of patients without overt diabetes mellitus but with diabetic glucose tolerance after recovery from the acute myocardial infarction is worse than that of patients with normal glucose tolerance (Wahlberg 1966)

A number of clinical characteristics are associated with the severity of the acute myocardial infarction according to Sievers (1963) and Weinblatt et al. (1968) and certain clinical observations during the hospitalization have furthermore been used for long-term prognostic estimations (Cole et al. 1954, Beard et al. 1960 White et al. 1960, Sievers 1963, Pell & D Alonzo 1964 Weinblatt et al. 1968) The association of impaired carbohydrate metabolism with an unfavourable outcome after myocardial infarction encouraged us to attempt to relate the clinical characteristics before and during the acute episode with the intravenous glucose tolerance under basal conditions in the patients of the present study In Chapters IV and V these clinical characteristics will also be considered in relation to long-term survival and to the effect of tolbutamide treatment.

Patients see Chapter I.

Methods see Chapter II.

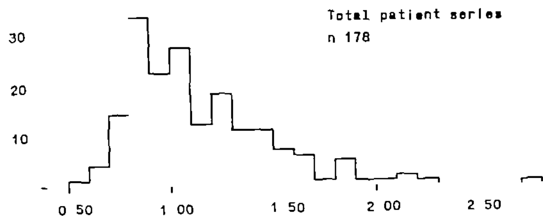
RESULTS

DISTRIBUTION OF IVGT

As seen in Fig. 2 the distribution of the k_g-values is asymmetrical, the chance of normality being 1 per cent ($P=0.01$) The mean k_g-value was 1 14, range 0 59—2.70 In Chapter II the grouping of the k_g values was presented (p 17) The number of patients with diabetic, borderline or normal IVGT is shown in Table 3 as are their mean ages and sex distribution.

The IVGT in male and female patients did not differ significantly

Among the male patients the IVGT groups did not differ as to age. More marked differences



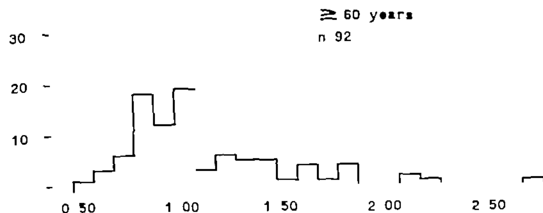




Fig 2 Distribution of the k_0 values Total series and subdivided according to age.

TABLE 5. Means and distributions of k values in relation to sex

	No of patients	Mean age	k_e value: Mean	k_e value: Range	IVGT Diabetic: No of patients	Diabetic: Per cent	Diabetic: Mean age	Borderline: No of patients	Borderline: Per cent	Borderline: Mean age	Normal: No of patients	Normal: Per cent	Normal: Mean age
Male	145	58	1 14	0.59—2 70	44	30	59	36	25	58	65	45	56
Female	33	66	1 15	0 61—2 27	8	24	71	13	40	67	1	36	63
Total	178	59	1.14	0.59—2 70	5	29	61	49	28	60	77	43	57

TABLE 6. Means and distributions of k values by age

Age	No of patients	Mean k_e value	IVGT Diabetic: No. of patients	Diabetic: Per cent	Borderline: No of patients	Borderline: Per cent	Normal: No. of patients	Normal: Per cent
≥70	26	0 98	12	46	9	35	5	19
50—69	120	1 16	34	28	31	26	55	46
<50	32	1 18	6	18	9	27	17	55

TABLE 7. Means and distribution of k-values in patients aged 59 or younger and 60 or older

Age	No of patients	Mean k_e-value	IVGT Diabetic: No. of patients	Diabetic: Per cent	Borderline: No. of patients	Borderline: Per cent	Normal: No. of patients	Normal: Per cent
<60	86	1 14	24	28	18	21	44	51
≥60	92	1 14	28	30	31	34	33	36

existed in women of corresponding ages and they were significantly greater in those with diabetic IVGT than in those with normal IVGT (71 and 63 years respectively $P<0.05$). For the total patient series the mean age of those with normal IVGT was significantly lower than that of the patients with diabetic as well as those with borderline IVGT (57, 61 and 60 years respectively $P<0.05$ in both instances) while the latter 2 groups did not differ in this respect.

Splitting the material into age groups led to differences in the distribution of the k_e values as shown in Table 6. The older patients more often exhibited diabetic and borderline values than the younger ones. The k_e values differed significantly when comparing those aged 70 or more with each of the 2 younger age groups ($P<0.05$) while the latter groups did not differ from each other. The mean ages of the patients under 70 with diabetic, borderline or normal k_e values differed maximally by one year, the mean ages being 57, 57 and 56 years, respectively. Fig. 2 also shows the distribution of the k values after dividing the material into those aged 60 and more and those younger than 60. As seen from Table 7 the percentages of normal k_e values differed in these 2 groups, but

TABLE 8 A. Clinical characteristics in 178 survivors from first myocardial infarction in relation to IVGT

	IVGT							
	Diabetic		Borderline		Normal		Total	
	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent
Total	52	*100*	49	*100*	77	*100*	178	*100*
Obese	28	*54*	27	*55*	28	*36*	83	*47*
Heredity								
Myocardial infarction	14	*27*	13	*27*	27	*35*	54	*30*
Diabetes	7	*13*	8	*16*	9	*12*	24	*13*
Ordinary physical activity								
Light	6	*12*	7	*14*	16	*21*	29	*16*
Moderate	35	*67*	33	*67*	46	*60*	114	*64*
Strenuous	11	*21*	9	*19*	15	*19*	35	*20*
Smoking and drinking								
Non smoker	19	*36*	19	*40*	23	*30*	61	*34*
Light	14	*27*	15	*30*	26	*34*	55	*31*
Heavy	19	*37*	15	*30*	28	*36*	62	*35*
No alcohol	8	*15*	13	*27*	20	*26*	41	*23*
Casual consumption	20	*38*	11	*22*	24	*31*	55	*31*
Regular	24	*47*	25	*51*	33	*43*	82	*46*
Cardiac functional capacity								
Group I	29	*56*	35	*71*	63	*82*	127	*71*
Group II—III	23	*44*	14	*29*	14	*18*	51	*29*
Pre-existing symptoms								
Angina pectoris	20	*38*	16	*33*	24	*31*	60	*34*
Hypertension	13	*25*	17	*35*	13	*17*	43	*24*
Congestive heart failure	6	*12*	5	*10*	2	*3*	13	*7*
Intermittent claudication	2	*4*	2	*4*	5	*6*	9	*5*
No pre-existing symptoms of CVD	22	*42*	22	*45*	47	*61*	91	*51*
Other features								
Pain at onset	51	*98*	47	*96*	75	*97*	173	*97*
Fever	26	*50*	26	*53*	34	*44*	86	*48*
Shock	3	*6*	4	*8*	8	*10*	15	*8*
Electrocardiography								
Mainly anterior infarction	20	*38*	24	*49*	46	*60*	90	*51*
Mainly posterior	28	*54*	19	*39*	27	*35*	74	*41*
Negative or uncertain location	4	*8*	6	*12*	4	*5*	14	*8*
VEB	15	*29*	22	*45*	21	*27*	58	*33*
SVEB or atrial fibrillation	18	*35*	12	*24*	23	*30*	53	*30*
*Major arrhythmias	16	*31*	12	*24*	13	*17*	41	*23*
Cardiac complications	30	*57*	32	*65*	45	*58*	107	*60*
SVEB atrial fibrillation and/or digitalis treatment	36	69	24	49	28	36	88	49
Acute treatment								
Anticoagulants	42	*81*	39	*80*	58	*75*	139	*78*
Antiarrhythmic therapy	2	*4*	3	*6*	2	*3*	7	*4*
Relative heart volume Normal	22	*50*	28	*64*	44	*70*	94	*62*
Abnormal*	22	*50*	16	*36*	19	*30*	57	*38*

*) Men >500 ml/m² BSA women >450 ml/m² BSA

TABLE 8 B Means and standard deviations (S.D.) of some clinical characteristics 178 survivors from first myocardial infarction in relation to IVGT

	IVGT							
	Diabetic		Borderline		Normal		Total	
	Mean	S D	Mean	S D	Mean	S D	Mean	S D
Age, years	61	11	60	10	57	9	59	10
Heighth, cm	175	8	171	8	172	7	173	8
Weight, kg	76	12	74	10	72	9	74	11
Laboratory tests[a]								
WBC 1000/mm³	13	4	13	5	12	3	13	4
ESR mm per hour	67	32	61	28	61	28	63	29
SGOT U/ml	177	110	151	101	15	90	16	99
SGPT U/ml	57	28	65	48	67	52	63	45
LDH U/ml	111	60	76	37	89	45	90	42
Relative heart volume, ml/m² BSA	501	111	454	80	451	84	466	93
Length of hospitalization, days	32	11	36	14	32	10	34	12

a) Maximum values during acute episode.

not significantly The respective mean k_c value of these 2 age groups was identical with that of the total series i.e. 1 14.

HEIGTH AND WEIGHT

The height and weight related to IVGT is shown in Table 8 B The male subjects with diabetic IVGT were taller than those with borderline and normal IVGT ($P<0\ 05$ in both instances) the figures being 177 175 and 174 cm respectively The latter 2 groups did not differ in this respect, nor did any of the female ones.

The male patients with diabetic IVGT were significantly heavier than those with normal IVGT ($P<0\ 05$) the figures being 78 and 74 kg respectively Those with borderline IVGT did not differ from the others in this respect. No such differences occurred in the females (Table 9)

According to the earlier given criteria for obesity (p 15) 36 per cent of the subjects with normal IVGT were classif ed as obese, which was significantly less than for those with diabetic and borderline IVGT 54 and 55 per cent obese, respectively ($P<0.05$ in both instances) More women than men were obese, or 67 and 42 per cent, respectively ($P<0\ 05$) Of the males, 32 per cent with normal IVGT were obese as compared with 52 per cent of those with diabetic IVGT and 47 per cent of those with borderline IVGT the former difference being significant ($P<0.05$) In the female patients there was no association between obesity and IVGT as also shown in Table 9

HEREDITY SMOKING, ALCOHOL, PHYSICAL ACTIVITY AND CARDIAC FUNCTION CAPACITY

Heredity for diabetes mellitus and myocardial infarction was not related to IVGT nor were the patients physical activity smoking or drinking habits during the decade preceding the myocardial infarction as seen in Table 8 A.

Cardiac functional capacity (p 15) had been sligthy or severely restricted in 44 per cent of the patients with diabetic IVGT compared w th 29 and 18 per cent of those with borderline and normal IVGT respectively the latter difference

TABLE 9 Mean height mean weight and obesity in relation to sex and IVGT

	IVGT					
	Male			Femal		
	Diabetic	Borderline	Normal	Diabetic	Borderline	Normal
Mean height, cm	177	175	174	163	162	162
Mean weight, kg	78	76	74	67	68	65
Per cent obese	52	47	32	62	77	58

being significant ($P<0.01$) These results were dependent on age as no such significant differences emerged in the patients less than 70 years old taken separately the corresponding figures being 32, 25 and 32 per cent, respectively

PRE EXISTING CARDIOVASCULAR SYMPTOMS

As is seen in Table 8 A pre-existing angina pectoris, congestive heart failure and intermittent claudication were not related to IVGT

Hypertension occurred in 25 and 35 per cent of the patients with diabetic and borderline IVGT respectively the latter percentage differing significantly from the 17 per cent found in those with normal IVGT ($P<0.05$) In subjects less than 70 years of age the corresponding figures were 25 40 and 17 per cent, the latter difference being also significant here ($P<0.01$) In patients with diabetic and borderline IVGT hypertension was more common in women than in men, the rates being 50 and 54 per cent for the women and 20 and 28 per cent for the men ($P<0.05$) In both sexes 17 per cent of the patients with normal IVGT had hypertension, which however, did not differ significantly from the rates in those with abnormal IVGT

The myocardial infarction was the first manifestation of cardiovascular disease in 61 per cent of the subjects with normal IVGT as compared with 42 per cent in those with diabetic IVGT the difference being significant ($P<0.05$) Among patients under 70 the former differed in this respect from both groups with abnormal IVGT ($P<0.05$)

PAIN AND FEVER

Pain or fever at the clinical onset of the myocardial infarction was not associated with IVGT

LOCATION OF THE MYOCARDIAL INFARCTION

The location of the infarction according to ECG was correlated to IVGT Among the patients with diabetic glucose tolerance 38 per cent had mainly an anterior infarction and 54 per cent mainly a posterior infarction, whereas the reverse was found in those with normal IVGT i.e. 60 and 35 per cent respectively ($P<0.05$) This difference remained unaltered after the exclusion of patients over 70 years of age. The frequencies of anterior and posterior infarctions in the patients with borderline IVGT were between those of the above mentioned groups without significant differences.

ARRHYTHMIAS

The arrhythmias registered were mainly grouped according to supraventricular (SVEB) or ventricular (VEB) origin. VEB were registered more often in patients with borderline IVGT than in those with normal IVGT i.e. or 45 per cent and 27 per cent, respectively ($P<0.05$) a difference not present if patients aged 70 or more were excluded The frequency in those with diabetic IVGT was 29 per cent. SVEB or atrial fibrillation as well as the incidence of "major arrhytmias" (p 15) bore no relation to IVGT A V block II—III occurred in 8 per cent, ventricular tachycardia in 2 per cent, and ventricular fibrillation in one per cent. Left or right bundle branch blocks were registered in 5 cases each, or a total of 12 per cent, again without relation to IVGT

OTHER CARDIAC COMPLICATIONS

The overall incidence of shock was 8 per cent, pulmonary edema 2 per cent, pericarditis 6 per cent, and a suspected extension of the infarction 4 per cent, while in 40 per cent no cardiac complications of any kind were registered. No association with IVGT was found.

OTHER CLINICAL CHARACTERISTICS

Among the patients with diabetic IVGT 69 per cent had had SVEB atrial fibrillation, and/or had received digitalis which was significantly higher than 49 and 36 per cent in the patients with borderline and normal IVGT ($P<0.05$ and $P<0.001$ respectively) The latter groups did not differ significantly in this respect. In patients below 70 years of age the corresponding rates were 63 43 and 33 per cent, respectively In this age group the incidence of SVEB atrial fibrillation and/or digitalis treatment was lower in the patients with normal IVGT than in those with diabetic, or diabetic plus borderline IVGT ($P<0.01$ and $P<0.05$ respectively)

Anticoagulants were given routinely and without differences between the IVGT groups

There was no difference in the use of antiarrhythmic therapy

The mean time of hospitalization did not differ between the IVGT groups.

LABORATORY TESTS AND HEART VOLUMES

The means of ESR, SGOT and LHD were higher in the diabetic IVGT group than in the 2 other groups as seen in Table 8 B but the difference was in no instance significant nor did WBC or SGPT differ

The heart volume was determined in 151 patients during the hospitalization and the values are seen in Table 8 A The patients with diabetic IVGT had abnormal relative heart volumes more often than those with normal IVGT i.e. 50 and 30 per cent respectively ($P<0.05$) The mean heart volume of the former patients was greater not only than that of the latter ones ($P<0.01$) but also than that of those with borderline IVGT ($P<0.05$) (Table 8 B)

DISCUSSION

DISTRIBUTION OF IVGT

The mean k_g-values of the male and female survivors from a first myocardial infarction were almost identical though 40 per cent of the female patients had borderline IVGT compared with 25 per cent of the males. Age was not related to IVGT in the males, whereas in the females glucose tolerance decreased with increasing age, which in the total series led to a significant age difference between the diabetic and borderline IVGT groups on comparison with the normal one In patients with cardiovascular disease a corresponding relation has been reported between age and IVGT (Wahlberg 1966) or age and OGT (Böhle & Schrade 1960 Kingsbury 1968) There are, however reports where this correlation has not been found (Aleksandrow et al 1962, Reaven et al 1963) possibly due to methodological factors (Kingsbury 1968) The distribution of the k_g-values in the patients aged 70 or more in the present series differed significantly from that of the younger ones, a difference which, on the other hand, was not present if the age limit was lowered to 60 After the exclusion of patients aged 70 or more no association between age and IVGT remained These circumstances are therefore taken into account when findings in relation to the IVGT are discussed in order to diminish a possible influence of age.

Since 1962, 8 studies of IVGT in subjects with coronary heart disease have been published, and the results of these investigations are summarized in Table 10 Several patients in the present study were included in a study published by Wahlberg (1966 5a in Table 10) Consequently this particular study is excluded in the lower part of the table

Only in 2 of the studies IVGT was determined in patients shortly after a myocardial infarction as in the present study (Nikkilä et al 1965 Rifkind 1966) while in the others were included subjects who had suffered earlier coronary occlusion (at least 3 years prior to test) or angina pectoris (Christiansen et al 1968) or had clinical and/or laboratory (Ryan et al 1967) or cinearteriographi

TABLE 10 Intravenous glucose tolerance in patients with cardiovascular disease results from 8 reports and the present study

	No of patients	Mean age	Glucose load, g	Mean k value	IVGT per cent: Abnormal: Diabetic	Borderline	Normal	Comments
1 Wahlberg (1962)	95	60	25	?	46	21	33	Cardiovascular disease
2 Brown (1963)	14	"Middle aged"	70[a]	?		28	78	CHD men only
3 Nikkila et al. (1965)	27	52 (?)	20	1 54		30	70[b]	Acute myocardial infarction
4 Rifkind (1966)	19	42	25	1 35		32	68[c]	Acute myocardial infarction
5a Wahlberg (1966)	190	61	25	1 10	29	31	40	Acute myocardial infarction
5b Wahlberg (1966)	160	57	25	1 19	30	23	47	Previous myocardial infarction
6 Ryan et al. (1967)	43	50	25	1 13	33	33	34[d]	CHD working men
7 Christiansen et al (1968)	25	55	25	1.23	24	24	52	CHD obese and hypertensives excluded
8 Heinle et al. (1969)	126	47 (?)	0 5/kg	?		67	33	CHD angiographically documented
A Total of (3 4, 6 & 7)	114	52 (?)		1.29				
B Total of (2—4, 6—8)	254	?		?		57	43	
C Total of 3 4, 5b, 6 & 7	274	54 (?)		1 23				
D Total of (2—4, 5b, 6—8)	414	?				61	39	
Present study	*178*	*59*	*25*	*1 14*	*29*	*28*	*43*	

[a]) According to Epstein (1967)
[b]) Normal k value ≥1.20
[c]) Criteria of the present study applied on fig 2
[d]) Estimated from their fig

cal evidence (Cohen et al. 1966 and extended by Heinle et al. 1969) of coronary heart disease. The results of Brown et al (1963) were published in the form of an abstract only in which the subjects studied were discribed as 14 middle aged men with ischemic heart disease As is seen in Table 10 the number of subjects studied has been small and the principles of selection regarding sex, age, physical fitness etc. variable. Differences the glucose load have probably been of minor importance (Wahlberg 1966) In some instances the information given has been somewhat scarce

From 4 of the studies (3 4 6 and 7 A in Table 10) totalling 114 patients, the mean k value could be estimated to be 1.29 which is rather higher than 1 14 in the present study The mean age of these subjects was approximately 52 years as compared to 59 years of the present series, which may explain the difference, as there is an inverse correlation between age and IVGT

As the earlier investigation of Wahlberg (1962) comprised a mixture of individuals with coronary heart and peripheral vascular diseases, this was not taken into account when the distribu

tion of IVGT was estimated in the preceding studies (*B* in Table 10) In the reports by Rifkind (1966) and Ryan et al. (1967) the exact figures were not given, but the distributions could be estimated from their figures. The total frequency of abnormal IVGTTs in all 254 subjects included in these investigations was 37 per cent, or identical with that of the combined diabetic and borderline IVGTTs in the study group. Finally if the 160 individuals with previous infarctions studied by Wahlberg (1966) were taken into account, none of which was included in the present study the overall frequency of abnormal IVGTTs was 61 per cent (*D* in Table 10) The mean k value of those studied, where it was given, was 1.23 and the mean age approximately 54 years (*C*)

From the above comparisons one might conclude that the IVGT of the study group seems to agree with those of smaller and in some instances less homogenous groups of subjects with coronary heart disease.

It can be added that Wahlberg (1966) when reviewing the literature on oral glucose tolerance in 590 patients with ischemic cardiovascular disease, found a remarkable agreement with the IVGT in a corresponding group of 530 patients investigated by him.

HEIGHT AND WEIGHT

The mean height of the men with diabetic IVGT in the present study was greater than that of those with borderline or normal IVGT No such tendency occurred in the female patients. Studies of male infarction patients have shown that these are shorter than controls (Gertler & White 1954, Hatch et al 1966) though this association has not been found by others (e.g Montenegro & Solberg 1968) The heights of adult diabetics are normal according to Joslin et al (1959) but body height has been found to be correlated inversely to the age at discovery of overt diabetes (De Moor & Meulepas 1968) From the figures of Reaven et al (1963) one can calculate that the patients with myocardial infarction with positive OGTT were 2 cm taller on average than those with negative OGTT the difference is, however not significant. Nor do the figures of another study yield any relations between body height and oral cortisone glucose tolerance (Hatch et al. 1966) Consequently the validity of the present findings is difficult to assess

Patients with normal IVGT weighed significantly less than those with diabetic IVGT in the present study and fewer of them were classified as obese, the latter difference also being significant in comparison with the prevalence of obesity in the borderline IVGT group A preponderance of obesity in subjects with coronary heart disease has been reported (Master et al. 1953) while others have failed to show this relationship (Gertler & White 1954, Montenegro & Solberg 1968) An explanation of the conflicting results may be found in the observations in the Framingham study (Kannel et al 1967) according to which overweight was associated with angina pectoris and sudden death but not with the development of myocardial infarction.

Obesity is associated with adult diabetes mellitus (Joslin et al 1959) as it also seems to be with abnormal oral or intravenous glucose tolerance in patients with coronary heart disease (Aleksandrow et al. 1962 Reaven et al. 1963 Hatch et al. 1966 and Wahlberg 1966) The findings of the present study thus seem to be in accordance with the results of other investigators. Women were as a whole more obese but without significant differences in this respect between the IVGT groups. Obesity was not age correlated in the present material.

Seven out of 20 survivors with overt diabetes excluded from the present study or 35 per cent were classified as obese. This rate did not differ from the prevalence of obesity in any of the 3 IVGT groups.

HEREDITY

It is generally accepted that overt diabetes mellitus in an inherited disease. CHD seems to prevail in certain families (Epstein 1964 but the role of genetics in this context is obscure The association between impaired glucose tolerance and

atherosclerosis is not reflected by the occurance of more diabetics in the family history of patients with myocardial infarction than in that of controls (Shanoff et al. 1961 Wahlberg 1966)

In the present study the occurrence of diabetes or myocardial infarction in first degree relatives was unrelated to IVGT The correspond ng rates in the excluded patients with overt diabetes were higher 6 out of 16 had diabetes and 8 myocardial *infarction in their family histories.*

SMOKING AND ALCOHOL CONSUMPTION

Cigarette smoking is associated with increased morbidity in myocardial infarction (Frank et al. 1966, Kannel 1966) while alcohol consumption does not show such a relation (Kannel 1966) Diabetes has not been reported to be related to these factors, even if smokers in the Tecumseh study tended to have higher blood sugar values (Epstein 1965) Keen et al (1965) did not find any correlation between smoking and OGT in the Bedford population study

In the present study no relationship was found between cigarette and alcohol consumption and IVGT in either sex.

PHYSICAL ACTIVITY

Epidemiological studies indicate a higher morbidity and mortality in persons who are less physically active than in more active ones (Morris et al 1966, Frank et al. 1966 Kannel 1967) Physical activity has beneficial influence on overt diabetics decreasing their insulin demand (Goldstein 1961) and physical activity has been claimed to improve glucose tolerance, but the evidenc is poor The insulin secretion is increased by moderate ergometer exercise in atherosclerotic subjects in contrast to no change in controls (Nikkilä et al. 1968) An association between IVGT and previous physical activity in survivors of a myocardial infarction which could have been expected did not occur in the present material.

CARDIAC FUNCTIONAL CAPACITY

The cardiac functional capacity was more restricted in patients with diabetic IVGT than in those with normal IVGT It appeared as if this difference was due to age, as after the exclusion of patients aged 70 or more it was no longer present. Furthermore, patients aged 60 or more yielded a significantly lower cardiac functional capacity than the younger ones ($P<0.05$) and as mentioned earlier the mean k_a values of these age groups were identical.

PRE EXISTING SYMPTOMS OF ARTERIAL DISEASE

In patients with angina pectoris or intermittent claudication the IVGT is the same as that of patients with myocardial infarction (Wahlberg 1966) This finding is in agreement with the observation of Kannel et al (1963) that the acute mortality in myocardial infarction in the general population is unaffected by pre-existing angina as it is in diabetics (Partamian & Bradley 1965) In contrast, other authors found an increased risk of early mortality in patients with pre-existing angina pectoris (Beard et al. 1960 Weinblatt et al. 1968) In the present series the prevalence of pre-existing angina pectoris and intermittent claudication was not related to IVGT and angina pectoris was also unrelated to OGT among the survivors from myocardial infarction studied by Datey and Nanda (1967)

Angina pectoris had been experienced by 7 out of 16 of the excluded patients with overt diabetes, i.e. a similar proportion to that in the present series.

A higher prevalence of hypertension independent of age was observed among the subjects with borderline IVGT A high blood pressure has been found in excess in diabetics (Pell & D Alonzo 1967 Ostrander et al 1965) Also in populations from which overt diabetics had been excluded hypertension was associated with hyperglycemia (Keen et al. 1965 O Sullivan et al. 1968) The findings of Keen et al (1965) indicated an association between blood pressure and oral glucose tolerance in persons with concomitant arterial diseases Nye (1964) reported an association between coronary heart disease and OGT in hypertensives, while Reaven et al (1963) Wahlberg (1966)

and Datey & Nanda (1967) found no relation between hypertension and glucose tolerance in subjects with coronary heart disease. If hyperglycemia is independently associated with ischemic arterial diseases and with hypertension as suggested by Ostrander et al. (1965) a combination of these diseases ought to increase the association with hyperglycemia. The findings of the present study and those of others contradict such a conclusion.

Two out of 16 diabetic survivors had hypertension compared with 24 per cent in the present series.

Myocardial infarction was the first manifestation of cardiovascular disease more frequently in patients with abnormal IVGT than in those with normal IVGT irrespective of age. Hospital studies, as well as autopsy materials, have shown evidence of earlier coronary atherosclerosis, peripheral vascular disease and hypertension more often in diabetics than in non-diabetics (Sternby 1968) which has also been confirmed in an epidemiological study of subjects with diabetes mellitus in Tecumseh (Ostrander et al. 1965) Moreover epidemiological evidence indicates that persons without overt diabetes with different manifestations of cardiovascular disease more often show hyperglycemia than do those without these manifestations (Ostrander et al. 1965) while the incidence of coronary heart disease is related to the level of blood sugar according to observations in the Framingham study (Epstein 1967 b)

PAIN

Painless infarction has been stated to be more common in diabetics than in non-diabetics (Bradley & Schonfeld 1962, Partamian & Bradley 1965) but in the present study infarction pain was unassociated with glucose tolerance as it was in the investigation by Datey & Nanda (1967)

LOCATION OF THE MYOCARDIAL INFARCTION

In 92 per cent of the cases the location of the myocardial infarction could be determined electrocardiographically and was considered to be mainly anterior in 51 per cent and posterior in 41 per cent. These frequencies seem to agree well with the findings generally reported (e.g. Bjerkelund 1957 Sorensen et al. 1968, Isomäki & Takala 1969) There was a significant difference in the distribution of the main site of the myocardial damage in relation to glucose tolerance, since in patients with normal IVGT infarction in the anterior wall region predominated, while in those with diabetic IVGT posterior infarction was commoner thus pattern being uninfluenced by age. In the subjects with borderline IVGT anterior infarctions were commoner than in those with diabetic IVGT but less frequent as compared with those with normal IVGT and for a posterior location the reverse was valid. Among the survivors excluded during the sampling because of diabetes mellitus, 14 out of 21 i.e. 67 per cent had a mainly anterior infarction and 24 per cent a posterior infarction which yielded a significant difference of distribution at comparison with patients of the study with diabetic IVGT ($P<0.05$) but with no other IVGT groups. Partamian & Bradley (1965) found that of 205 diabetic patients with first infarctions 54 per cent had anterior and 23 per cent posterior infarction (9 mixed and 40 subendocardial infarctions were not included, nor early deaths, but location had no influence on short-term survival, nor significantly on the long-term survival)

The reason for this tendency in patients who had suffered from posterior infarctions to have diabetic IVGT in contrast to those with anterior ones who more often had normal IVGT is hard to explain, particularly as patients with overt diabetes did not seem to differ in this respect from what is generally seen in infarcted patients. Exclusion of anterolateral and posterolateral infarctions did not decrease the significant association of infarction location to the IVGT

ARRHYTHMIAS

Since 1963 investigations with ECG monitoring after acute myocardial infarction have shown the true incidence of arrhythmias to be considerably higher than the frequencies reported earlier based on occasional ECG tracings.

Though the occurrence of arrhythmias in the present study was in agreement with those reported by Julian et al (1961) Stock et al. (1967) Lown et al. (1967) and Mogensen (1970) it is likely that, for VEB which occurred approximately twice as frequently in the reports of continous monitoring, routine and non systematic ECG recordings might only expose greater differences in their occurence.

When the data of the present material were being analyzed, Lown and his collaborators (1967 1969) suggested a physiological grouping of the arrhythmias during the acute myocardial infarction. Criticism by James (1968) has been answered by Lown (1969) In the present study VEB and ventricular tachyarrhythmias have been regarded as indicating electrical instability while SVEB and atrial fibrillation (no atrial flutter registered) constituted signs of pump failure, the latter being the only arrhythmias out of those indicating this failure according to Lown and his collaborators studied here. The borderline IVGT group had a higher incidence of VEB than the normal IVGT group but an effect of age could not be excluded as this difference was no longer present when only patients below 70 were considered. The incidence of SVEB or atrial fibrillation was not related to IVGT *The rates of arrhythmias in those 21 excluded survivors with overt diabetes at Serafimerlasarettet were similar to those of the study group*

OTHER CLINICAL CHARACTERISTICS

Although not reported in each instance in the hospital records it seemed reasonable to consider incipient or manifest heart failure as the main indication for digitalis administration. These patients were therefore brought together with those in which SVEB or atrial fibrillation occurred. It was found that the number of patients with one or more of these charateristics indicating pump failure was significantly higher in the group with abnormal glucose tolerance compared with that with normal glucose tolerance irrespective of age. Previously it was found that SVEB or atrial fibrillation was equally common in all IVGT groups. This appears to imply that clinically manifest heart failure was more common in the patients with abnormal glucose tolerance while signs of latent heart failure were evenly distributed in relation to IVGT

Antiarrhythmic drugs were ordered infrequently during the hospital stay and without relation to IVGT

LABORATORY TESTS AND HEART VOLUMES

The short-term prognosis has been shown to be associated with a number of laboratory findings according to Sievers (1963) He found the mortality to increase with a rise of temperature, WBC and SGOT while ESR was uncorrelated. Others have not observed some of these correlations (e.g. Eckerström 1951) An association between the size of the infarct and the maximum level of SGOT and LDH has been demonstrated (Ruegsegger et al. 1959 Kibe & Nilsson 1967) In the present study there was a tendency towards higher maximal values of ESR, SGOT and LDH in patients with diabetic IVGT compared with the other groups, but the differences were not significant. Patients with diabetic IVGT had enlarged hearts more often than those with normal IVGT while in comparison with the borderline IVGT group the mean relative heart volume only differed but not the distribution of normal or abnormal *relative heart volumes.*

COMMENTS

Hence, the findings in the case histories of survivors from a first myocardial infarction related to IVGT have been in agreement with earlier observations with respect to the association between glucose tolerance and body weight (Wahlberg 1966) and the presence of pre-existing cardiovascular symptoms (Ostrander et al 1965) The relationship between glucose tolerance and height, location of the infarction, relative heart volume and symptoms and therapy suggestive of heart failure does not appear to have been investigated or reported earlier Datey & Nanda (1967) probably did not relate the latter features and parameters to glucose tolerance as their statement reads "No significant differences in the presence or absence of pain, shock, angina, hypertension or electrocardiographic abnormalities were detected between normo-glycemic and the hy

perglycemic (infarction) patients Therefore the findings of the present study are not necessarily contradictory to theirs Hypertension and VEB occurred more often among patients with borderline IVGT than among those with a diabetic or normal IVGT The difference between the borderline and normal groups only was significant. This might reflect less positive associations between these clinical characteristics and glucose tolerance. On the other hand, with a great number of comparisons, the statistical possibility of getting false positive or negative results is not negligible. Perhaps less caution need be shown when interpreting the other significant differences between the IVGT groups as these tended to be progressive.

In Chapter V the prognostic implication of these findings will be studied

CONCLUSIONS

Hence, one might conclude, that in survivors from a first myocardial infarction those with diabetic IVGT are taller and fatter have pre-existing arterial symptoms, posterior infarction and presence of heart failure and enlargement more often than those with normal IVGT

LONG-TERM TOLBUTAMIDE TREATMENT
THE EFFECT UPON SURVIVAL AND CARDIOVASCULAR SYMPTOMS AFTER MYOCAR DIAL INFARCTION SIDE EFFECTS

INTRODUCTION

Oral antidiabetic treatment with tolbutamide was introduced in 1955 Reports on its beneficial effect on symptoms of atherosclerotic cardiovascular disease have been published subsequently In 1958 Fabrykant reported an alleviating effect on angina pectoris in diabetic patients after institution of tolbutamide therapy and in 1960 similar results were arrived at in patients, some of whom were non-diabetic, with angina pectoris and/or intermittent claudication (Fabrykant & Ashe 1960) Singh and Bardhan (1959) and Fearnley et al. (1960) made corresponding observations, and beneficial effect was reported also in non-diabetic patients with thromboangiitis obliterans (Singh & Brara 1960) or intermittent claudication and angina pectoris (Singh et al. 1962)

Although Clarke and Naylor (1961) could not confirm this effect of tolbutamide in patients with peripheral arterial disease and intermittent claudication, most observations in the literature seemed to indicate a favourable effect of tolbutamide on certain symptoms of cardiovascular disease. Further support for a possible connection was given by reports of abnormal glucose tolerance being common also in subjects with coronary heart disease but without overt diabetes mellitus (Edelmann 1934, Raab & Rabinowitz 1936, Goldberger et al. 1945 Böhle & Schrade 1960 Waddell & Field 1960 Aleksandrow et al. 1962, Sowton 1962)

In 1963 preliminary results of a study then in progress at Serafimerlasarettet (Wahlberg 1966) furthermore indicated an adverse influence of abnormal carbohydrate tolerance upon long term survival after an acute myocardial infarction.

The above associations prompted a controlled study of the effect of tolbutamide on the mortality of survivors from a first myocardial infarction. At the same time the influence of this treatment in relation to intravenous glucose tolerance as well as other parameters could be studied.

Patients see Chapter I

Methods see Chapter II.

GROUPING OF PATIENTS

SELECTION

As presented in Chapter II the participants were allocated to a tolbutamide or a control group according to their birth date. The characteristics of the 2 groups are given in Tables 11 12 and 20 and Figs 3 and 4.

The 2 groups showed no statistically significant differences in composition and were thus com-

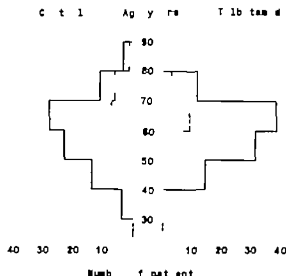


Fig 3 Age distribution of the total material i decades Actual ge range from 37 to 82 years (control) and 41 to 77 years (tolbutamide) respect vely The broken lines denote female patients.

TABLE 11 A. Clinical characteristics in 178 survivors from a first myocardial infarction in relation to treatment

	Control		Tolbutamide	
	No. of patients	Per cent	No of patients	Per cent
Total	83	*100*	95	*100*
Obese	38	*47*	45	*48*
Heredity				
Myocardial infarction	4	*29*	30	*32*
Diabetes	13	*16*	11	*12*
Ordinary physical activity				
Light	13	*16*	16	*17*
Moderate	50	*60*	64	*67*
Strenuous	20	*4*	15	*16*
Smoking and drinking				
Non smoker	29	*35*	32	*34*
Light	26	*31*	29	*30*
Heavy	28	*34*	34	*36*
No alcohol	20	*24*	21	*22*
Casual consumption	4	*29*	31	*33*
Regular	39	*47*	43	*45*
Cardiac functional capacity				
Group I	62	*75*	65	*68*
Group II—III	21	*25*	30	*32*
Pre-existing symptoms				
Angina pectoris	27	*33*	33	*35*
Hypertension	20	*24*	3	*4*
Congestive heart failure	8	*10*	5	*5*
Intermittent claudication	1	*1*	8	*8*
No pre-existing symptoms of CVD	46	*55*	45	*47*
Other features				
Pain at onset	80	*96*	93	*98*
Fever	44	*53*	42	*44*
Shock	9	*11*	6	*6*
Electrocardiography				
Mainly anterior infarction	45	*54*	45	*47*
Mainly posterior	29	*35*	45	*47*
Negative or uncertain location	9	*11*	5	*16*
VEB	27	*33*	31	*33*
SVEB or atrial fibrillation	25	*30*	28	*30*
Major arrhythmias	20	*24*	21	*22*
Cardiac complications	47	*57*	60	*63*
SVEB, atrial fibrillation and/or digitalis treatment	45	*54*	43	*45*
Acute treatment				
Anticoagulants	64	*77*	75	*79*
Antiarrhythmic therapy	4	*5*	5	*5*
Relative heart volume Normal	39	*62*	55	*63*
Relative heart volume Abnormal	24	*38*	33	*37*

) Men >500 ml/m² BSA women >450 ml/m² BSA

TABLE 11 B. Means and standard deviation (S.D.) of [illegible] clinical characteristics 178 survivors from a first myocardial infarction in relation to treatment

	Control		Tolbutamide	
	Mean	S D	Mean	S D
Height, cm	173	8	173	8
Weight, kg	74	10	74	11
Laboratory tests)				
WBC 1000/mm³	13	5	13	5
ESR mm per hour	61	29	63	31
SGOT U/ml	157	95	167	104
SGPT U/ml	62	41	65	49
LDH U/ml	101	53	79	37
Relative heart volume, ml/m² BSA	465	90	467	97
Length of hospitalization, days	34	15	33	11

) Maximum values during acute episode

parable as to age, physical and clinical characteristics as well as to carbohydrate tolerance measured with IVGTT

OBSERVATION TIME

The observation time ranged from 1 year to 5.5 years. The tolbutamide group was observed during 275 person years, and the control group during 250 person years, or on average 2.9 and 3.0 years per patient respectively

WITHDRAWALS

Three patients withdrew from the follow-up, 2 in the tolbutamide group after 3 and 22 months, respectively and one control after 14 months. One committed suicide, another moved abroad and the third patient for unknown reason failed to appear

RESULTS

TOTAL MORTALITY

The total number of deaths during the study was 29 Sixteen patients, or 19 per cent, died in the control group and 13 i.e. 14 per cent, in the

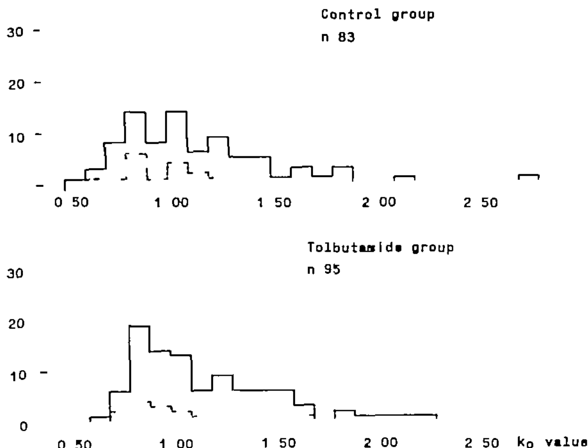


Fig 4 Distribution of the k_0-values. Broken lines denote patients who died during the follow-up

TABLE 12. Mean age and k_0-values in relation to sex and tolbutamide treatment

				IVGT								
				Diabetic			Borderline			Normal		
	No of patients	Mean age	Mean k_0-value	No of patients	Per cent	Mean age	No of patients	Per cent	Mean age	No of patients	Per cent	Mean age
Control												
Male	67	57	1 14	22	33	59	17	25	55	28	42	56
Female	16	69	1 15	4	25	75	5	31	72	7	44	63
Total	83	59	1 14	26	31	61	22	27	59	35	42	58
Tolbutamid												
Male	78	58	1 13	22	28	60	19	24	61	37	48	56
Female	17	61	1.17	4	24	68	8	47	63	5	29	62
Total	95	59	1 14	26	27	61	27	29	62	42	44	57

TABLE 13. Total mortality and m an ges in relation to sex and tolbutamide treatment

	Control			Tolbutamide			Total		
	No. of patients	Per cent	Mean age	No. of patients	Per cent	Mean age	No. of patients	Per cent	Mean age
Male	12	*18*	61	11	*14*	63	23	*16*	62
Female	4	*25*	72		*12*	69	6	*18*	71
Total	16	*19*	64	13	*14*	64	29	*16*	64

TABLE 14 Diagnostic idence f fatal myocardial reinfarctions during the study in relation to treatment

	Number of deaths		
	Control	Tolbutamide	Total
Confirmed at autopsy	12	11	23
Clinical evidence without autopsy	2	1	3
Sudden death without autopsy		1	3
Total	16	13	29

TABLE 15 Cumulative survival ate total mortality and mean survival tim in elation to tolbutamide treatment total patient serie

Observation time, months	Control *A*	*B*	*C*	Tolbutamide *A*	*B*	*C*
0— 6	83	12	0.835	95	2	0 977
7—1	71	3	0 818	9	4	0 936
13—18	61	0	0.818	88	1	0 924
19— 4	54	0	0 818	69	2	0.896
25—30	44	1	0 799	60	2	0 880
31—36	38	0	0 799	51	1	0 861
37—42	31	0	0.799	38	1	0 835
43—48	19	0	0 799	29	0	0 835
49—54	18	0	0.799	18	0	0 835
55—60	13	0	0.799	9	0	0 835
61—66	6	0	0 799	7	0	0.835
0—66						
Number		16			13	
Per cent		*19*			*14*	
Mean survival time, months		6			18*	

) $P<0\ 01$

A Alive at beginning of period

B Died during period

C. Cumulative proportions surviving through period

tolbutamide group, as seen in Table 13 This diffe rence in mortality rate was not significant.

The mean age of those who died was 64 years at the time of the myocardial infarction irrespective of treatment compared with 58 years of the long-term survivors ($P<0.05$)

All deaths were considered to have been car diac, though the amount of evidence varied. The information obtained about the mode of death is summarized in Table 14

Chest pain prior to the fatal reinfarction had been experienced by 17 of the deceased patients 10 controls and 7 patients in the tolbutamide group. I each of thes groups, 4 subjects died suddenly and information about the mode of death was missing in 2 subjects. The mode of death bore no relation to IVGT

CUMULATIVE SURVIVAL RATE

Table 15 and Fig. 5 show the cumulative sur vival rates of the total series using the life table method of Cutler and Ederer (1958) Over 18 months following the myocardial infarction 15 controls died compared with 7 patients in the tolbutamide group ($P<0.05$)

The mean survival time was 6 months for those who died n the control group compared with 18 months in the tolbutamide group ($P<0\ 01$) The dissimilar distribution of mortality is also illustrated by the proportion of patients dying within the first 21 months, i.e. 15 out of 16 deceased controls, compared with 7 out of 13 in the tolbutamide group ($P<0.05$)

The observation times of the patients who died or survived are summarized in Table 16. The diffe rence is significant ($P<0.001$)

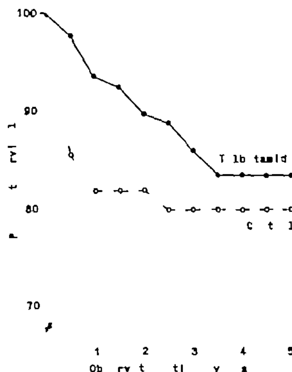


Fig 5 Cumulative survival in the total material.

TABLE 17 First recurrent myocardial infarction in relation to tolbutamide treatment total series

	Control (=83)			Tolbutamide (=95)		
Observation time, months	Non-fatal	Fatal	Total	Non-fatal	Fatal	Total
0—6	5	10	15	1	2	3
7—12	0	3	3	2	4	6
13—18	0	0	0	0	1	1
19—24	0	0	0	1	2	3
25—66	1	1	2	1	3	4
0—66						
Number	6	14	20	5	12	17
Per cent			*24*			*18*
Mean observation time, months	10	7	8	16	13	16

NON-FATAL AND FATAL FIRST RELAPSES

The non-fatal first myocardial reinfarctions were evenly distributed in the tolbutamide and the control groups as were the fatal ones (Table 17) A similar mean delay before non fatal relapse occurred could also be observed in the former group i.e. 16 months as compared with 10 months in the controls. In the latter group 4 out of 6 such relapses occurred within a month after discharge from hospital, while 4 months passed until the first non-fatal relapse was seen in the former group

The mean time elapsing until the first myocardial reinfarction—fatal or non fatal—occurred was longer in the tolbutamide group than in the control group i.e. 16 and 8 months, respectively ($P<0.01$) The incidence of a first relapse within the first 22 months was 10 out of a total of 19 in the tolbutamide group, which was less than 18 out of a total of 20 among controls ($P<0.05$)

TABLE 16 Total survival time in relation to total observation time and treatment

	Years of observation		
	Dead	Alive	Total
Control	46	204	250
Tolbutamide	16	259	275
Total	62	463	525

SEX AND SURVIVAL

There was no sex difference in cumulative survival rates in either treatment group as illustrated in Table 18. The overall survival rate of the men in the tolbutamide group did not differ from that of the control group but death was postponed in the former group compared with controls over the first six months, similar to that seen in the total series ($P<0.01$)

In all 11 men died in the tolbutamide group 5 of them within the first 8 months as compared with 10 out of 12 controls within the same time period ($P<0.05$) Their mean survival times were 18 and 6 months, respectively ($P<0.05$) The corresponding figures in the women were too small for statistical analysis.

TABLE 18. Cumulative survival rates total mortality and mean survival time in relation to sex and tolbutamide treatment

Observation time, months	Males						Females					
	Control			Tolbutamide			Control			Tolbutamide		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
0—6	67	9	0.866	78	–	0.974	16	3	0.813	17	0	1.0
7—12	58	2	0.836	73	3	0.935	13	1	0.731	17	1	0.941
13—24	55	0	0.836	72	3	0.886	12	0	0.731	16	0	0.941
25—66	38	1	0.812	48	3	0.808	6	0	0.731	1	1	0.859
0—66												
Number		12			11			4			2	
Per cent		18			14			25			1	
Mean survival time, months		6*			10*			—			—	

*) $P<0.05$

A. Alive at beginning of period

B. Died during period

C. Cumulative proportions surviving through period

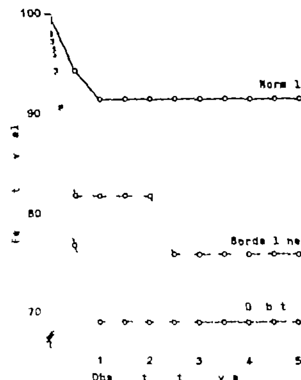


Fig. 6. Cumulative survival in the control group in relation to IVGT

IVGT AND SURVIVAL

Control group

The long-term survival in relation to IVGT in the controls is shown in Table 19 and Fig. 6

The mean k_c value of the dead in the control group was 0.95 i.e. lower than the 1.19 of the survivors ($P<0.05$) as illustrated in Fig 3. The overall survival rate was 91 per cent in the group with normal IVGT compared with 77 and 69 per cent in those with borderline and diabetic IVGT respectively. The normal IVGT group differed in this respect from the 2 abnormal ones combined, i.e. 73 per cent ($P<0.05$)

Tolbutamide group

The mean k_c-value of the dead was 0.97 as compared with 1.16 of the survivors ($P<0.05$) as also illustrated in Fig 3.

The total survival rate in the normal IVGT group was 95 per cent which was significantly higher than the corresponding 79 per cent in the abnormal IVGT group ($P<0.05$). The mean length of survival of the deceased in the diabetic and

TABLE 19 Mean ages, cumulative survival rates, total mortality and mean survival time in relation to IVGT and tolbutamide treatment

Control	Diabetic (61 yrs)			Borderline (59 yrs)			Normal (57 yrs)		
Observation time, months	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
0—6	26	6	0.769	2	4	0.818	35	2	0.943
7—12	20	2	0.692	18	0	0.818	33	1	0.914
13—24	18	0	0.692	17	0	0.818	32	0	0.914
25—66	10	0	0.692	11	1	0.760	20	0	0.914
0—66									
Number		8			5			5	
Per cent		31			23			9	
Mean survival time, months		5			9			6	
Tolbutamide	Diabetic (61 yrs)			Borderline (61 yrs)			Normal (57 yrs)		
Observation time, months	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
0—6	26	2	0.923	27	0	1.0	42	0	1.0
7—12	24	3	0.808	27	0	1.0	41	1	0.976
13—24	21	1	0.740	7	2	0.921	40	0	0.976
25—66	10	0	0.740	2	3	0.785	28	1	0.926
0—66									
Number		6			5			2	
Per cent		23			19			3	
Mean survival time, months		10*			6			23	

*) $P<0.05$

A Alive at beginning of period

B Died during period

C. Cumulative proportions surviving through period

borderline IVGT groups also differed from each other ($P<0.05$) as shown in Table 19.

In Fig. 7 the cumulative survival rates in the 2 treatment groups have been correlated to the IVGT. In patients with abnormal IVGT the mean survival time of the deceased in the tolbutamide group differed from that of the controls, i.e. 17 and 7 months, respectively ($P<0.05$) but not in the diabetic or borderline IVGT groups separately on corresponding comparisons. The proportion of controls with abnormal IVGT who died during the first observation year i.e. 12 out of in all 13 deaths was greater than corresponding 5 out of 11 in the tolbutamide group ($P<0.05$). All 4 patients in the tolbutamide group who died during the first 11 months had a diabetic k_g-value (range 0.77—0.87) which was significantly lower than the k_g values (mean 1.04, range 0.82—1.61) of those who died later ($P<0.05$). In the control group no such trend was observed.

Patients less than 70 years old

To enable a separate analysis of survival in relation to IVGT in subjects under 70 the 2 treatment groups were fused.

From Table 20 it is apparent that the total survival rate of the patients with normal IVGT was higher than that of the patients with diabetic IVGT as well as that of the total number of those with abnormal IVGT ($P<0.05$ in both instances). The survival rate of the patients aged 70 and more was lower than that of the younger ones in the

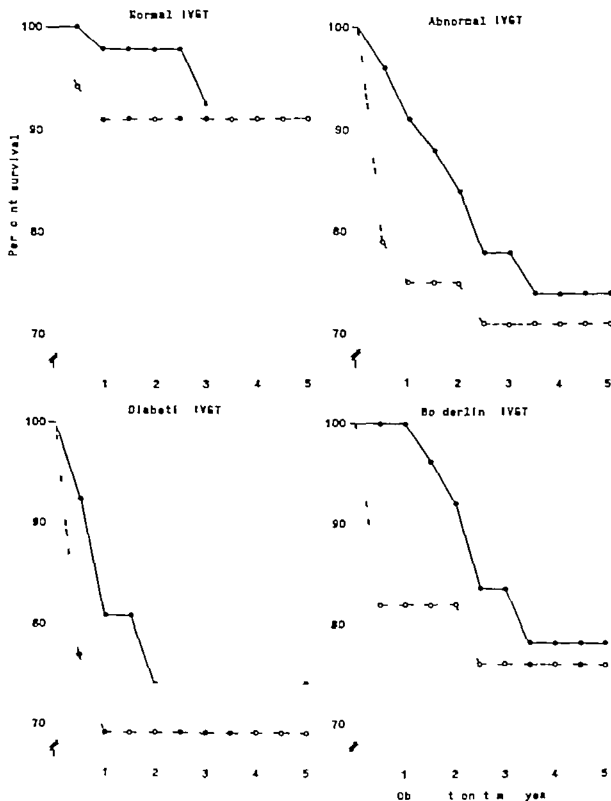


Fig Cumulativ surv al in relation to IVGT
o — o control group ● — ● tolbutamide group

TABLE 20 Mean ages, cumulative survival rates and total mortality in relation to IVGT in patients less than 70 years of age

Observation months	Diabetic (57 yrs)			Borderline (57 yrs)			Normal (56 yrs)		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
0—6	40	3	0.925	40	2	0.950	72	2	0.972
7—12	37	5	0.800	38	0	0.950	69	2	0.944
13—24	32	1	0.739	37	1	0.921	67	0	0.944
25—66	17	0	0.739	32	2	0.862	43	0	0.944
0—66									
Number		9			5			4	
Per cent		22*			12			6*	

*) $P<0.01$

A: Alive at beginning of period

B. Died during period

C. Cumulative proportions surviving through period

TABLE 21 Cardiovascular symptoms at the last clinical visit during the follow-up in relation to treatment and IVGT

	Treatment				IVGT					
	Control		Tolbutamide		Diabetic		Borderline		Normal	
	No. of patients	Per cent	No. of patients	Per cent	No of patients	Per cent	No. of patients	Per cent	No of patients	Per cent
Overall survivors	67	100	82	100	38	100	39	100	72	100
Angina pectoris	20	30	24	29	12	32	9	23	23	32
Cardiac functional capacity										
Total series										
Group I	37	55	48	59	15	39*	23	59	47	65*
Group II—III	30	45	34	41	23	61	16	41	25	35
Less than 70 years	58	100	76	100	31	100	35	100	68	100
Group I	36	62	48	63	15	48	23	66	46	68
Group II—III	22	38	28	37	16	52	12	34	22	32

*) $P<0.05$

total patient group ($P<0.001$) This difference was evident also in patients with borderline IVGT ($P<0.05$) separately but not in the 2 other IVGT groups.

CARDIOVASCULAR SYMPTOMS AND REHABILITATION

As seen in Table 21 the presence of angina pectoris during the follow-up period was unrelated to treatment or IVGT The same was true of intermittent claudication. Concerning cardiac functional capacity there was a difference between those with initially diabetic IVGT and those with normal IVGT ($P<0.05$) In patients less than 70 this difference was not significant, however

Table 22 illustrates the total percentage of those returning to active employment after rehabilitation. This was uninfluenced by tolbutamide treatment. However 6 out of 7 subjects in the tolbutamide group who subsequently died resumed work

TABLE 22 Mortality and reactivation of occupationally active patients when suffering first myocardial infarction in relation to tolbutamide treatment

	Control (n=83)		Tolbutamide (n=93)	
	No. of patients	Per cent	No. of patients	Per cent
Occupationally active	61	*100*	69	*100*
Died				
before resuming work	6	*10*	1	*1*
after	3	*5*	6	*9*
Disablement pension or retirement	8	*13*	11	*16*
Reactivated at the end of the follow up	44	*7*	51	*4*

compared with 3 out of 9 controls, the total time of active work being 70 and 21 months, respectively ($P<0.05$)

SIDE EFFECTS

In Table 23 complaints considered suggestive of *hypoglycemia* at the 3 months visit or later are listed Such symptoms occurred in 19 per cent of the controls as compared with 41 per cent in those treated with tolbutamide. ($P<0.01$) In the latter patients no difference was seen regarding the appearence of hypoglycemic symptoms between subjects with normal or abnormal IVGT A *drug rash* was experienced by only one patient who belonged to the control group No serious hypoglycemic complications were seen throughout the study

Symptoms leading to a lowering of dosage were 0 14 per patient year in the tolbutamide group and 0 07 in controls.

Forty-eight per cent of the patients in the tolbutamide group with borderline or normal IVGT had their dose lowered some time during the follow-up as compared with 33 per cent among those with diabetic IVGT but this difference was not significant. In 1 out of 38 patients, in whom the dosage had been lowered, i.e. 32 per cent, the ordinary intake of one gram of tolbutamide was later reverted to

Consequently in 28 per cent or 26 out of initially 93 patients, it was considered necessary to keep the tolbutamide dosage submaximal, usually 0 75 g Among those with abnormal IVGT the corresponding rate was 19 per cent. In 3 subjects more than 0 5 g in divided doses appeared to induce hypoglycemia symptoms. The mean dose per patient during the whole follow-up period was 0 90 g tolbutamide daily No other side-effects were observed.

Laboratory investigations which were performed in order to detect signs indicative of tolbutamide induced toxic effects on the liver thyroid or blood, did not show any such effect.

BODY WEIGHT

In Table 24 the body weights at the last IVGTTs have been expressed in percentages of the weights at the start of the study and set in relation to the IVGT both at the start and at the last retest, on an average 2.8 years later No significant changes were noticed

DISCUSSION

The findings indicate a beneficial effect of prolonged tolbutamide treatment on survival over a period extending 18 months after the acute episode of a first myocardial infarction, but not on overall survival rate over 5 years. The total survival rates in the control and tolbutamide groups were 81 and 86 per cent, respectively while the mean survival times of those who died were 6 and 18 months, respectively

Wahlberg (1966) showed the long-term prognosis after myocardial infarction to be adversely influenced by abnormal glucose tolerance. These observations were confirmed by the findings in the control group. Normal IVGT implied a good prognosis per se, and the improvement induced by tolbutamide treatment was significant only in those patients with abnormal IVGT The postponement of a fatal outcome seemed to be greater in the survivors with initially borderline IVGT than in those with a diabetic, but the difference was not statistically significant. Those who died were older

TABLE 23 Hypoglycemic symptoms during follow-up causing reduction in dosage of research medication

	Number of patients					Total		Temporary adjustment	
	Attending 3 month clinic visit	Hunger only	Cold sweating	Cardiac symptoms	Hypoglycemic syndrome[a]	No. of patients	Per cent	No of patients	Per cent
Control									
Diabetic	24	3	1	—	2	6	*25*		
Borderline	20	2	1	—	—	3	*15*		
Normal	33	5	—	1	—	6	*18*		
Total	77	10	2	1	2	15	*19*		
Tolbutamide									
Diabetic	24	2	1	4	1	8	*33*	2	*25*
Borderline	27	9	—	1	5	13	*48*	2	*15*
Normal	42	9	3	3	2	17	*48*	8	*47*
Total	93	20	4	8	6	38	*41*	12	*32*

[a]) Combinations of e g hunger nervousness, weakness, or the above symptoms relieved by carbohydrate intake

TABLE 24 Body weight at last retest in per cent of initial weight in relation to IVGT and tolbutamide treatment

IVGT	Control			Tolbutamide		
	Diabetic	Borderline	Normal	Diabetic	Borderline	Normal
At start	99 0	98 6	99 4	95.5	99 9	99 2
At last retest	97.2	99 6	100 3	98.1	101 4	98 2

than the surviving patients, but the effect of the treatment was independent of age and sex.

The treatment also appeared to diminish the incidence of non-fatal relapses.

On the other hand, prolonged tolbutamide treatment did not seem to influence other manifestations of cardiovascular diseases, i.e. angina pectoris, functional cardiac capacity intermittent claudication.

Though symptoms suggesting hypoglycemia had been reported at least once by nearly half of the patients on tolbutamide, no serious side-effects were observed during the follow-up

SURVIVAL

The long-term survival after an acute myocardial infarction varies considerably in different series, often possibly because of varying criteria used in selecting patients As a number of exclusions were made from the study group of the present investigation, this also represents a certain selection and consequently its mortality rates have to be compared with those of corresponding reports.

From Sievers (1963) presentation of 1584 survivors from a first myocardial infarction survival rates can be estimated to be 80 75 70 and 65 per cent during the first 4 years, respectively The corresponding percentages in 170 controls studied by Harvald et al. (1962) were 84, 82 and 70 surviving during 3 years of observation. In an investigation of anticoagulant treatment by Lovell et al. (1967) the annual fractions surviving were 88 81 and 76 per cent in 178 men forming a control group These rates agree on the whole with the corresponding annual survival rates of the present series, i.e. 82, 82 80 80 and 80 per cent

respectively A comparison was also made with the long-term survival after a first myocardial in farction during the 5 years preceding the start of the present study There were 171 such patients from 1958 through 1962, their corresponding sur vival rates being 87 77 71 65 and 61 per cent. It is apparent that the survival rate of the control group was somewhat lower during the first year after discharge from hospital but not after 2 years. The above comparisons indicate that the long term survival rate of the control group is comparable to other series of myocardial infarction.

No preventive pharmacological treatment nor dietary or hygenic measures has as yet been gene rally accepted because of controversial results of trials in this field Some controlled investigations of various long-term treatment of survivors from a myocardial infarction initiated immediately at the patient s discharge from hospital as in the present series will be discussed in the following.

ANTICOAGULANT TRIALS

Favourable results in controlled studies on mor tality of long-term anticoagulant treatment have been reported by Bjerkelund (1957) Aspenström & Korsan-Bengtsen (1964) U.S. Veterans Ad ministration (1965 Ebert 1969) Lovell et al. (1967) Borchgrevink et al. (1968) Sorensen et al (1968) Similar benefit has not been found by Clausen et al. (1961) Harvald et al. (1962) Second Report to Med cal Council (1964) Seaman et al (1969) Some of the findings have been difficult to compare however owing to differences in design and conduct of the trials.

Reviews have been given among others by Mc Michael & Parry (1960) and an International anti coagulant review group (1970)

Bjerkelund (1957) in a study of 237 men noticed a significant reduction in mortality (from 13 per cent to 3 per cent) in men less than 60 years old during the first year after their infarction, not thereafter Aspenstrom & Korsan Bengtsen (1964) found a difference n survival only in poor risk patients over 60 The U S Veterans Administra tion trial (1965 Ebert 1969) of a selected group comprising 747 men showed a s gnificant reduction in mortality rate in the first 3 years but not thereafter This difference was significant in men aged 55 and younger only but not in those over 55 Differences in cumulative annual survival rates ranged between 3 and 8 per cent. The same finding of age limited benefit was made by Lovell et al. (1967) in a study of 350 men, treated with "high dose" or low dose" phenprocoumon. The cumulative survival of the former group after 2 years was 92 per cent as compared with 83 per cent of the latter After 3 years this difference disappeared. In a study of 159 female patients under 70 during the first year after a myocardial infarction Borchgrevink et al. (1968) mortality was reduced in those aged 60 to 69 Death rates were 3 per cent for the treatment group and 12 per cent for the control group In another recently published study of 234 short-term survivors of myocardial infarction Sorensen et al. (1968) achieved a significant decrease in mortality with anticoagulant treatment in "bad risk patients During an average observa tion time of 2 years in this category the mortality in the treatment group was 11 per cent compared with 22 per cent in the control group. The total mortality was 9 and 19 per cent, respectively

Clausen et al. (1961) found no change in sur vival in a study of 192 patients nor could Har vald et al. (1962) in a treated group of 145 pa tients compared with another group of 170 pa tients who received a placebo, though at the end of the first year of follow-up the death rates were 10 and 16 per cent respectively Age grouping did not alter the overall finding. In the Second report to the Medical Research Council (1964) of a controlled trial of long-term anticoagulant therapy in 383 patients the overall mortality was not significantly altered during 3 years of treatment. In men below 55 years of age there were 18 deaths among 69 men on low dosage as compared with 9 out of 74 on high dosage, but again this difference was insignificant. Seaman et al. (1969) could in their final report only confirm an earlier negative result of double-blind anticoagulant treatment undertaken for an average time of 6 years. One main difference of this study from the above studies was a delay of more than 8 weeks after the acute myo-

cardial infarction for almost a third of the patients before entering the *trial (range 3—80 months)*

Lovell et al. (1967) also studied the effect of heparin in the same category of patients as discussed above. Intermittent injection therapy was not found to alter the mortality rate.

After these conflicting results it seems possible that the benefit of anticoagulant treatment can be found chiefly in the treatment of survivors in their fifties and younger for one to 2 years after the acute episode of myocardial infarction. However according to a recent report an international anticoagulant review group could still not reach complete agreement whether long-term anticoagulant treatment after a myocardial infarction prolonged survival. The group arrived at this conclusion after an analysis of the records of 2205 male and 282 female patients included in 9 controlled trials. (International anticoagulant review group 1970)

HORMONE TRIALS

An extensive survey of hormone and diet trials has been given by Oliver (1967) Oestrogens have been shown to depress elevated plasma cholesterol levels, and long-term trials of their effect on recurrence after recovery from an acute myocardial infarction have been made Oliver and Boyd (1961) Marmorston et al. (1962) and Stamler et al. (1963) The former 2 investigators gave ethinyl oestradiol to 50 male good risk survivors. During the 5 year study there were 10 deaths from *myocardial infarction in the control group* and 13 in the oestrogen group

Marmorston et al. (1962) found a temporary reduction in the mortality of men under 55 years during the first 2 years of treatment with premarin of 78 male infarction survivors. No changes occurred in groups simultaneously treated with ethinyl oestradiol or mytatrienediol.

Stamler et al. (1963) studied the effect of oestrogen in 275 men under 50 of whom 263 had recovered from myocardial infarction. The 5 year mortality was significantly reduced in 84 poor risk but not in 166 good risk patients including most of the men with single infarcts. In the latter 2 trials the numbers of withdrawals were, however, *not negligible.*

The serious side-effect compared with the modest benefit ought to rule out oestrogens as a drug for long-term treatment.

DIET TRIALS

Dietary treatment starting after the acute episode of myocardial infarction seems to be of little benefit to long-term survival. In a study of low fat diet on 264 men aged under 65 in London (Report of Research Committe 1965) no significant reduction in mortality was achieved over 3 years. Borchgrevink et al. (1966) found no difference in mortality when comparing a group given linseed oil with another one given corn oil during an observation period of on average 10 months in 200 men of whom all but 12 had had recent myocardial infarction.

Another British controlled trial concerned with diet also yielded no improvement in survival after myocardial infarction (Report of Research Committee 1968) In 393 male patients aged under 60 who had recovered from their first myocardial infarction 25 deaths occurred in each of the numerically equal experimental groups during an observation time varying from 2 to nearly 7 years. Dietary measures of the kind reported above do not seem to reduce the first year's mortality after myocardial infarction.

CARDIOVASCULAR SYMPTOMS AND REHABILITATION

Reports of a favourable effect upon clinical manifestations in diabetic and later in non-diabetic individuals with ischemic cardiovascular diseases from tolbutamide treatment (Fabrykant 1958, Singh & Bardhan 1959 Fabrykant & Ashe 1960 Fearnly et al 1960 Singh et al. 1962) prompted the institution of antidiabetic treatment in the present study when it was found that a majority of survivors from a myocardial infarction exhibited abnormal IVGT In the present series prolonged tolbutamide treatment, however did not appear to exert a beneficial influence upon cardiovascular manifestations such as angina pectoris, intermittent

respectively A comparison was also made with the long-term survival after a first myocardial infarction during the 5 years preceding the start of the present study There were 171 such patients from 1958 through 1962, their corresponding survival rates being 87 77 71 65 and 61 per cent. It is apparent that the survival rate of the control group was somewhat lower during the first year after discharge from hospital but not after 2 years The above comparisons indicate that the long-term survival rate of the control group is comparable to other series of myocardial infarction.

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Favourable results in controlled studies on mortality of long-term anticoagulant treatment have been reported by Bjerkelund (1957) Aspenström & Korsan-Bengtsen (1964) U.S. Veterans Administration (1965 Ebert 1969) Lovell et al. (196) Borchgrevink et al. (1968) Sorensen et al (1968) Similar benefit has not been found by Clause et al (1961) Harvald et al. (1962) Se ond Report to Medical Council (1964) Seaman et l (1969) Some of the findings have been d ff ult to ompare however owing to differences n des g and conduct of the trials.

Rev ew ha been given among others by Mc Michael & Parry (1960) and an International anti coagulant rev ew group (1970)

Bjerkelund (195) in a study of 237 men noticed a significant eduction in mortality (from 13 per cent to 3 pe ent) in men less than 60 years old during the f rst year after their infarction, not thereafter Aspenst om & Korsan-Bengtsen (1964) found a differen survival only in poor-risk patients over 60 The U S Veterans Administration trial (1965 Ebert 1969) of a selected group comprising 747 men show d a s gnificant reduction in mortality rate in the first 3 years but not thereafter. This difference was significant in men aged 55 and younger only but not in those over 55 Differences in cumulative annual survival rates ranged between 3 and 8 per cent. The same finding of age limited benefit was made by Lovell et al. (1967) in a study of 350 men, treated with "high dose or low dose phenprocoumon. The cumulative survival of the former group after 2 years was 92 per cent as compared with 83 per cent of the latter After 3 years this difference disappeared. In a study of 159 female patients under 70 during the first year after a myocardial infarction Borchgrevink et al. (1968) mortality was reduced in those aged 60 to 69 Death rates were 3 per cent for the treatment group and 12 per cent for the control group In another recently published study of 234 short-term survivors of myocardial infarction Sorensen et al. (1968) achieved a significant decrease in mortality with anticoagulant treatment in "bad risk patients During an average observation time of 2 years in this category the mortality in the treatment group was 11 per cent compared with 22 per cent in the control group The total mortality was 9 and 19 per cent, respectively

Clausen et al. (1961) found no change in survival in a study of 192 patients nor could Harvald et al. (1962) in a treated group of 145 patients compared with another group of 170 patients who received a placebo though at the end of the first year of follow-up the death rates were 10 and 16 per cent respectively Age grouping did not alter the overall finding. In the Second report to the Medical Research Council (1964) of a controlled trial of long term anticoagulant therapy in 383 patients the overall mortality was not significantly altered during 3 years of treatment. In men below 55 years of age there were 18 deaths among 69 men on low dosage as compared with 9 out of 74 on high dosage, but again this difference was insignificant. Seaman et al (1969) could in their final report only confirm an earlier negative result of double-blind anticoagulant treatment undertaken for an a erage time of 6 years One main difference of this study from the above studies was a delay of more than 8 weeks after the acute myo-

CONCLUSIONS

Tolbutamide treatment appears to prolong survival comparable with that achieved in the most favourable reports on anticoagulant treatment.

Glucose tolerance testing seems to offer one specific means of detecting a risk group among clinically non-diabetic subjects surviving a first myocardial infarction. The cumulative survival rate in the present study over a period extending for 5 years was 92 per cent in those with normal IVGT but 75 per cent in those with abnormal IVGT. Tolbutamide treatment reduced the death rate significantly in the latter group for one and a half years following the myocardial infarction.

Moreover prolonged tolbutamide treatment did not induce serious side-effects throughout the study. Other manifestations of cardiovascular disease were mainly unaffected by this treatment during the whole follow-up period.

LONG-TERM TOLBUTAMIDE TREATMENT; CLINICAL CHARACTERISTICS OF PROGNOSTIC VALUE

INTRODUCTION

An association between a number of clinical characteristics and glucose tolerance has been established in the past as well as in the present study (Chapter III). Also long-term prognosis after a myocardial infarction has been related to IVGT (Wahlberg 1966) a finding which again was confirmed in the present study (Chapter V). The nature of the relationship of abnormal glucose tolerance to adverse prognosis after myocardial infarction remains unexplained.

Observations during the acute period of a myocardial infarction suggest that pre-existing hypertension and angina pectoris as well as certain arrhythmias during the hospital stay influence the long term survival unfavourably (Cole et al. 1954, Honey & Truelove 1957 White et al 1960 Sievers 1963 Pell & D'Alonzo 1964, Weinblatt et al. 1968). Hence an investigation of the interrelationship between prognosis, clinical characteristics and IVGT was thought to be valuable because an understanding of this could give further information about risk factors in this context. It was also of interest to know the influence of tolbutamide treatment upon clinical characteristics which have been shown to be of importance in the assessment of prognosis, because it had been found to prolong survival time.

The control group was studied separately and the results thereafter related to those in the tolbutamide group.

Patients see Chapter I

Method see Chapter II

CONTROL GROUP

RESULTS

Only the clinical characteristics found to be associated with long-term prognosis are listed in Tables 25 and 26 and no mention is therefore made of the remaining ones discussed in Chapter IV. In each category of patients with any of these clinical characteristics, the mean ages of those who subsequently died were generally higher than those of the survivors, though insignificantly in all instances.

In Table 25 it can be seen that in patients, in whom *VEB SVEB or atrial fibrillation* or *"major arrhythmias"* had been registered, the overall mortality rate was about 40 per cent, while it ranged between 9 and 13 per cent in patients without them. The risk ratios thus ranged between 4.6 and 3.2 ($P<0.01$ $P<0.01$ $P<0.05$ respectively). The risk ratio of those with *cardiac complications* was 3.3 and their long-term mortality rate was 27 per cent ($P<0.05$). *SVEB atrial fibrillation and/or digitalis treatment* present in 45 controls, seemed particularly important regarding the long-term prognosis. When these 45 were excluded the death rate fell from 33 to 3 per cent, as 15 out of 16 who died subsequently belonged to this group. The risk ratio was 12.8 ($P<0.01$). The cumulative survival rates are illustrated in Figs. 8—12.

From the previous paragraph it is evident that the relationship of VEB to mortality could not be studied independently of SVEB atrial fibrillation and/or digitalis treatment as only one patient who died was without this latter characteristic. When VEB occurred also, however the overall mortality was 11 out of 21 (52 per cent) compared with 4 out of 24 controls (17 per cent) when this combination was not present ($P<0.05$) as illustrated in Fig. 13.

The inherent risk in these clinical characteristics was closely related to IVGT and a separate analysis of this could only be carried out in the *controls with abnormal IVGT* owing to the small

TABLE 25 Certain clinical characteristics during hospitalization of prognostic significance in relation to tolbutamide treatment total series

	Control (n=83)					Tolbutamide (n=95)				
	Total		Deaths			Total		Deaths		
	No. of patients	Per cent	No of patients	Per cent		No. of patients	Per cent	No of patients	Per cent	
VEB	27	33	11	41		31	33	4	15*	
No VEB	56	67	5	9		64	67	9	14	
Risk ratio					4 6					0 9
P					<0 01					N S.
SVEB or atrial fibrillation	25	30	10	40		28	29	10	36	
No SVEB or atrial fibrillation	58	70	6	10		67	71	3	4	
Risk ratio					3.9					8.0
P					<0 01					<0 001
Major arrhythmias	20	24	8	40		21	22	5	24	
No major arrhythmias	63	76	8	13		74	78	8	11	
Risk ratio					3.2					2.2.
P					<0.05					N.S.
Cardiac complications	47	57	13	27		60	63	11	18	
No cardiac complications	36	43	3	8		35	37	2	6	
Risk ratio					3 3					3.2
P					<0 05					<0 05
SVEB atrial fibrillation and/or digitalis treatment	45	54	15	33		43	45	12	28	
No SVEB atrial fibrillation or digitalis treatment	38	46	1	3		52	55	1	2	
Risk ratio					12 8					14.5
P					<0 01					<0 001

) *P*<0 05

number of deaths (3) in the remaining normal ones From Table 26 it is apparent that the risk ratios were similar for all the patients in the study but significant only in controls who had had either VEB SVEB or atrial fibrillation, or SVEB atrial fibrillation and/or digitalis treatment, i.e. 4.1 4.3 and 7 9 respectively ($P<0.01$ $P<0.05$ $P<0.01$ respectively) while the mortality rates were higher, or 53 62 and 41 per cent, respectively The cumulative survival rates are illustrated in Figs. 8—12

The mean relative heart volume in controls with SVEB atrial fibrillation and/or digitalis treatment during the hospitalization was 471 ml/m² BSA, which did not differ from those without this characteristic, i.e. 458 ml/m² BSA. As no one had received research medication at the time of heart volume determination, the same comparison in all patients of the present study was also made, and then significant differences appeared, the volumes being 493 and 437 ml/m² BSA, respectively ($P<0.001$) The difference between the mean heart volumes of those who died, i.e. 547 ml/m² BSA, and those who survived and had had SVEB atrial fibrillation and/or digitalis, i.e. 463 ml/m² BSA, was significant ($P<0.01$) but not in the controls, i.e. 512 and 449 ml/m² BSA, respectively

A total of 16 controls died during the follow-up period Ten had experienced chest pain, 4 others

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Risk ratio. The ratio between the death rates in the presence or absence of certain clinical characteristic

TABLE 26 Certain clinical characteristics during hospitalization of prognostic significance in relation to tolbutamide treatment in patients with abnormal IVGT

	Control (=48)					Tolbutamide (=53)				
	Total		Deaths			Total		Deaths		
	No. of patients	Per cent	No. of patients	Per cent		No. of patients	Per cent	No. of patients	Per cent	
VEB	17	35	9	53		20	38	4	20	
No VEB	31	65	4	13		33	62	7	21	
Risk ratio					4.1					0.9
P					<0.01					N.S.
SVEB or atrial fibrillation	13	27	8	61		17	32	9	53	
No SVEB or atrial fibrillation	35	73	5	14		36	68		6	
Risk ratio					4.3					9.5
P					<0.05					<0.01
Major arrhythmias	15	31	7	47		13	5	5	38	
No major arrhythmias	33	69	6	18		40	75	6	15	
Risk ratio					2.6					.6
P					N.S.					N.S.
Cardiac complications	28	58	11	39		34	64	10	29	
No cardiac complications	[illegible]0	42	2	10		19	36	1	5	
Risk ratio					3.9					5.6
P					N.S.					N.S.
SVEB atrial fibrillation and/or digitalis treatment	29	60	12	41		31	58	10	32	
No SVEB, atrial fibrillation or digitalis treatment	19	40	1	5		2	42	1	5	
Risk ratio					7.9					7.1
P					<0.01					<0.01

died suddenly and in 2 information was missing. No significant correlation between the mode of death and any of the clinical characteristics or IVGT was detected

DISCUSSION

A consideration of clinical characteristics in controls prior to the acute myocardial infarction and during the acute episode revealed certain arrhythmias to be associated with a poor long-term prognosis The absence of cardiac complications was usually favourable and the absence of SVEB atrial fibrillation and/or digitalis treatment particularly so. No others were found to affect the prognosis.

A number of investigators have tried to identify those clinical characteristics which could predict long-term prognosis

In the present study *hypertension* was not associated with an adverse long term prognosis, which is contrary to what is generally reported in the literature. (Cole et al. 1954 Honey & True love 1957 Beard et al. 1960 White et al. 1960 Sievers 1963 Pell & D Alonzo 1964, Weinblatt et al. 1968) The study by Weinblatt et al. is particularly informative as it is prospective. Hypertension occurred in 24 per cent of male survivors from a first myocardial infarction in their study as compared with 22 per cent of the present study Thus, even though the incidences of hypertension is in

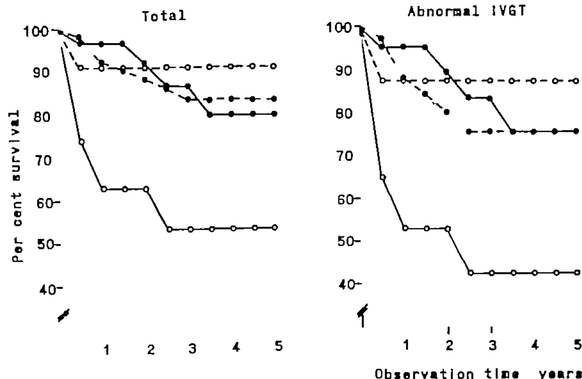


Fig. 8 Cumulative survival in relation to VEB and tolbutamide treatment: total material and patients with abnormal IVGT

Treatment Clinical characteristic

control • tolbutamide — present absent

essence identical the prognostic implications differ Varying definitions and composition of patient groups may have played roles, however

Pre-existing angina pectoris was of no influence on long term prognosis in the present study which is in agreement with Cole et al. (1954) and Honey & Truelove (1957) but not with Weinblatt et al. (1968) I their study angina pectoris had occurred in only 13 per cent of the men surviving the acute attack for at least one month as compared with 34 per cent in the present study The reliability of this symptom in their study may ha e been greater and therefore of better predictive value.

The nonsignificance of *physical activity* and *smoking* prior to the myocardial infarction in the present study is in agreement with the findings of Weinblatt et al. (1968) It is also of interest that factors such as height, weight, and pre-existing symptoms of cardiovascular disease as well as the location of the myocardial infarction, which in the preceding Chapter were found to be associated with IVGT had no relation to the long-term prognosis.

It is also of interest that no reports exist as yet about the association of *arrhythmias* detected by continuous ECG monitoring during the acute episode with long-term prognosis. Our present knowledge is based on results from other routine procedures Cole et al. (1954) found long-term survival to be decreased in the presence of bundle branch block, atrioventricular block and/or ectopic rhythms, i.e. SVEB VEB and auricular fibrillation in a series comprising patients with first myocardial infarctions from 1932 through 1941 According to observations in a series from 1940 to 1954

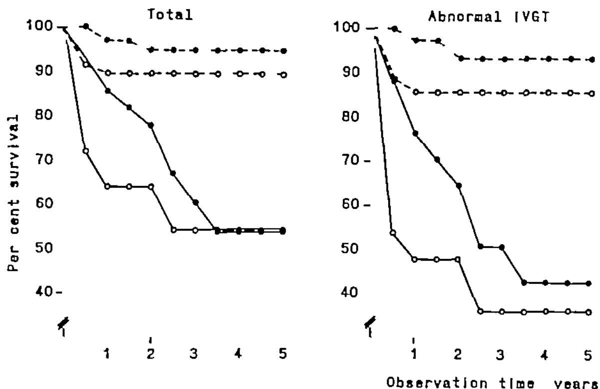


Fig 9 Cumulative survival in relation to SVEB or atrial fibrillation and tolbutamide treatment: total material and patients with abnormal IVGT Symbols as in Fig 8

reported by Honey & Truelove (1957) arrhythmias, i.e auricular fibrillation or flutter, or multiple extrasystoles were bad long-term prognostic features Beard et al. (1960) found that ventricular and supraventricular arrhythmias had an adverse effect upon 5-year mortality White et al. (1960) found that the occurrence of frequent premature contractions, atrial or ventricular tachyarrhythmias, or heart block influenced the one year outcome adversely According to Stock et al. (1967) and Denborough et al (1968) major arrhythmias, defined as sino-atrial, bundle branch, incomplete or complete A V blocks, and ventricular supraventricular tachycardia or fibrillation, also affected long-term prognosis adversely The findings of all these reports seem to agree with the results of the present study in which certain supraventricular and ventricular arrhythmias were associated with shorter survival Using the modified criteria of "major arrhythmias (p 15) it was observed that the presence of this characteristic affected adversely the long term prognosis of the control group too The predictive value of this combination of arrhythmias seemed to be similar to those observed for cardiac complications, SVEB or atrial fibrillation, or VEB, during the acute episode

As discussed in Chapter III (p 31) Lown and his collaborators (1967 1969) suggested a physiological grouping of the arrhythmias during acute myocardial infarction, and this appears to be the first time anyone has related the arrhythmias to the underlying clinical situation. In the present study SVEB and atrial fibrillation were the only recorded arrhythmias which indicated pump failure On the other hand, in a prognostic evaluation it seemed natural to extend this group to all patients treated with digitalis, because digitalis has heart failure and supraventricular tachyarrhythmias as its main indications. It also appeared, that one or more of these clinical characteristics, i.e. SVEB, atrial fibrillation and/or digitalis treatment had been present in all but one of the

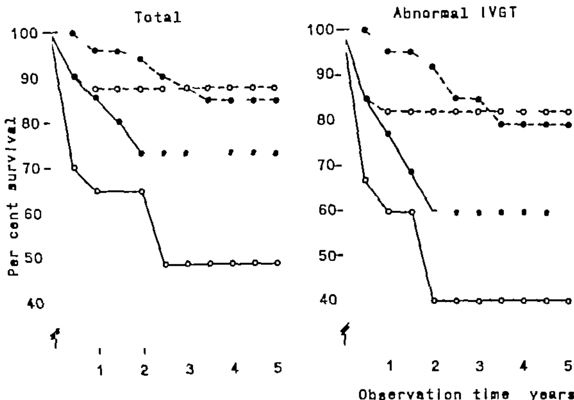


Fig 10. Cumulativ survival in relation to major arrhythmias and tolbutamide treatment; total material and patients with abnormal IVGT Symbols as in Fig 8

controls who died, and consequently indicated shorter long-term survival. Sievers (1963) when using the classification by Helander (1949) observed, that patients aged 60 and more who survived a mild infarction had lower mortality rate 2—3 years after the acute episode than those with severe infarction ($P<0.05$) The influence of heart failure on prognosis was not studied separately Weinblatt et al. (1968) did not find severe infarction, characterized by the occurrence of overt cardiac failure, shock, ventricular tachycardia or complete heart block to imply a poor long-term prognosis. High peak values of serum enzymes (Kibe & N'lsson 1967) and enlarged relative heart volumes (Warts et al. 1966) have been reported to be related to an adverse long-term prognosis, both findings being considered to indicate the extent of myocardial disease. A corresponding comparison of the peak serum enzymes or of enlarged heart volumes did not yield an association with overall survival the present series The mean relative heart volume of the controls who died was insignificantly greater than that of the survivors. However, this difference was significant in the total series.

Lown et al (1967 1969) among others have suggested ventricular ectopic beats of different types to predispose to ventricular fibrillation. VEB seems to influence the long-term prognosis adversely too (Cole et al. 1954, Beard et al. 1960) and recent epidemiological evidence from Tecumseh (Chiang et al. 1968) of premature beats recorded on occasional ECGs has stressed its prognostic significance. In the Tecumseh study the origin of these ectopics was ventricular in 61 per cent, atrial in 21 nodal in 4, or combined in 5 per cent (9 per cent were not classified) They were correlated to manifest coronary disease, and during an average follow-up period of 4 years 4.2 per cent of the subjects with premature beats died compared with 0.83 per cent without this finding ($P<0.001$) A good agreement in the distribution

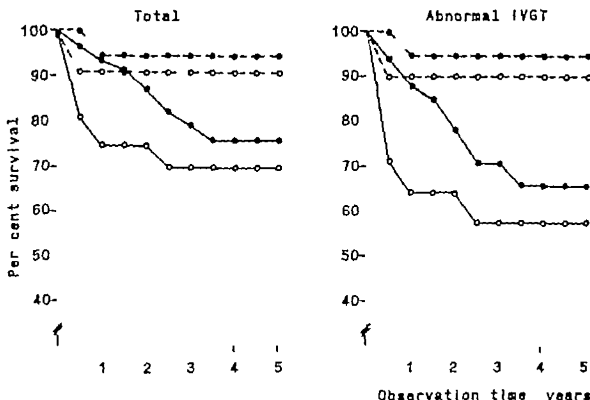


Fig. 11. Cumulative survival in relation to cardiac complications and tolbutamide treatment: total material and patients with abnormal IVGT. Symbols as in Fig. 8.

of the origin of the above premature beats with that of the present series is illustrated by the incidence of VEB being 49 per cent, SVEB 5 per cent, and combined in 26 per cent.

The mode of death (p. 36) bore no significant relationship to any of the clinical characteristics discussed or to IVGT. This seems not to be in agreement with the findings of Lovell (1969) according to whom patients having had major arrhythmias died a sudden death significantly more often than did those without these arrhythmias.

When evaluating the present results, it must be remembered that the information regarding arrhythmias, cardiac complications and digitalis treatment relied on data from retrospective investigation of hospital records. Moreover, the routine for ECG recording had neither been uniform nor systematic. There may be a bias, too, as clinically more severely looking patients are prone to have more frequent ECGs and chest X-rays taken. The additional facilities to obtain information by continous monitoring during the acute myocardial infarction will enable a further evaluation of the findings.

However, according to the present findings, cardiac complications during the acute stage of a first myocardial infarction suggest an adverse long-term prognosis. Highly predictive in this respect were signs suggesting heart failure, i.e. SVEB, atrial fibrillation and/or digitalis treatment.

The overall survival rate was 81 per cent and in those with abnormal IVGT 73 per cent. The only clinical characteristic that was associated both with abnormal IVGT and an adverse long-term prognosis was the presence of SVEB, atrial fibrillation and/or digitalis treatment during hospitalization for the acute myocardial infarction. The occurrence of the latter implied a survival rate of 77 per cent, and a combination of them and abnormal IVGT reduced survival rate to 59 per cent, as illustrated in Table 26 and Fig. 12. In controls with abnormal IVGT in whom also VEB had been registered the overall survival rate was further

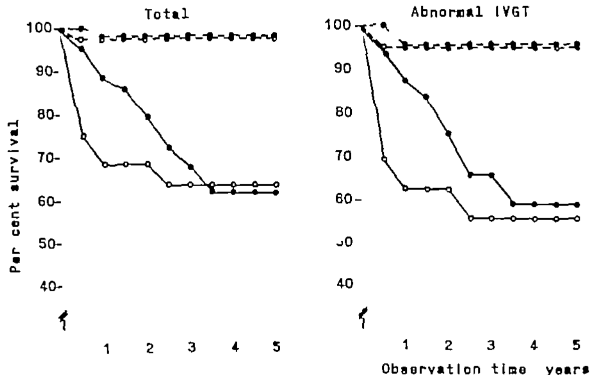


Fig 12. Cumulativ survival in relation to SVEB atrial fibrillation and/or digitalis treatment total material and patients with abnormal IVGT Symbols as in Fig. 8.

lowered to 31 per cent and cumulative survival at 2 5 years became 19 per cent, as shown in Fig. 13

Ettinger et al. (1968) suggested the glucose intolerance observed in patients with ischemic car diovascular disease not to be confined to such car diac patients but common for the majority of compensated cardiac subjects with a reduced car diac output and therefore to be interpreted as an acquired rather than a genetically determined meta bolic disorder In an investigation of 28 clinically compensated patients without ischemic cardiovascular disease the IVGT was found to be reduced in 60 per cent, i e. to a similar extent as observed in patients with ischemic cardiovascular disease. The cardiac index was abnormal in 23 out of 24 subjects investigated, while IVGT was abnormal in 15 and normal in 9 (according to their Fig. 6) though no statistically significant relationship emerged. A majority of 13 patients showed a d minished insulin response differing from that of controls. It was proposed that this might be due to increased sympathetic activity seen in cardiac patients with advanced cardiac disease (Chidsey et al. 1965) and the effect of catecholamines in reducing insulin secretion by the pancreas (Porte et al. 1966 b) They therefore infused norepi nephrine during an IVGTT in 4 normal individuals and observed a decline in glucose tolerance and plasma insulin to levels seen in cardiac patients. No information concerning catecholamine excretion is given in these latter patients The authors con cl ded that other factors may contribute to a greater extent than the circulatory status.

In order to elucidate the relationship between IVGT and the cardiac state as investigated by phy sical working capacity on a bicycle ergometer (Sjöstrand 1960) (p 16) and the relative heart volume (Liljestrand et al. 1939) 47 patients of the present series were studied.

The criteria used for selection were similar age, sex, and follow-up time in arbitrarily chosen individuals from the tolbutamide and the control

TABLE 27. Physical working capacity and relative heart volume in 47 patients during the follow-up in relation to IVGT

	IVGT	
	Abnormal	Normal
Total number	21	6
Men	16	25
Women	5	1
Mean age, years	63	63
Mean follow-up time, years	3.0	2.7
Mean relative heart volume, ml/m² BSA	479	413
Men only	481	433
Results		
Maximal pulse rate when in steady state	123	170
Total physical working capacity, kgf	4222	4131

) n=25
) Equivalent to *kil pond meter (kp m)*

groups. The characteristics and results are given in Table 27. At the time of the test 21 of them had abnormal IVGT and 26 normal IVGT. All were in sinus rhythm and 6 patients in each IVGT group were receiving digitalis treatment. No differences were observed between these 2 subgroups regarding physical working capacity which also was unrelated to tolbutamide treatment. These findings do not seem give support to the assumption by Ettinger et al. (1968) of a correlation between cardiac decompensation and abnormal IVGT.

TOLBUTAMIDE GROUP

RESULTS

As in the control group the overall survival was significantly lower in the patients with *SVEB* and/or *atrial fibrillation* ($P<0.001$) taken separately as well as after the addition of those who had received digitalis ($P<0.001$) as shown in Table 25. The one-year survival rate for tolbutamide-treated patients with *SVEB, atrial fibrillation and/or digitalis treatment* on the other hand was significantly higher, i.e. 38 out of 43 or 86 per cent, than in the control group, i.e. 31 out of 45 or 69 per cent ($P<0.05$) as illustrated in Fig. 1., and a total of 12 of the 13 dead patients had had this latter combination of clinical characteristics. Moreover in such patients observed for at least 24 months 12 out of 27 controls, i.e. 44 per cent, died compared with 4 out of an equal number of tolbutamide-treated ones, i.e. 15 per cent ($P<0.05$).

Regarding the occurrence of *cardiac complications* there was no difference in total mortality between the tolbutamide-treated patients and the controls, but over 18 months the survival rate was higher in the former group, i.e. 35 out of 60 who survived compared with 35 out of 47 controls ($P<0.05$) (Fig. 11).

As seen in Table 25 and Figs. 8 and 10 the overall survival rate of the tolbutamide-treated patients was uninfluenced by *VEB* or *"major arrhythmias"* occurring during hospitalization in contrast to findings in the control group. Furthermore, in the patients with VEB the overall survival in the tolbutamide group was significantly better than in the control group ($P<0.05$) but not in those with major arrhythmias.

Eleven of the 13 patients who died had *abnormal IVGT* and a separate analysis of the clinical characteristics upon prognosis in relation to abnormal IVGT is shown in Table 26 and illustrated in Figs. 8—12. The results are similar to those in the total tolbutamide group, but as in the controls cardiac complications were no longer of prognostic significance. There was no difference in survival between the patients with SVEB or atrial fibrillation and the corresponding controls, while the total survival of those with VEB was higher, i.e. 16 out of 20 surviving compared with 8 out of 17 controls ($P<0.05$).

The presence of SVEB, atrial fibrillation and/or digitalis treatment implied a reduced chance of survival, i.e. 32 per cent, but during the first 1 months survival was better than in corresponding controls, as 27 out of 31 in the tolbutamide group survived compared with 18 out of 29 controls ($P<0.05$).

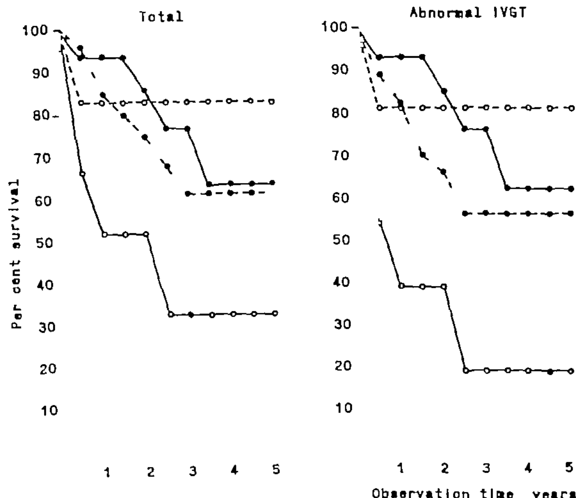


Fig 15 Cumulative survival in patients with SVEB, atrial fibrillation and/or digitalis treatment in relation to VEB and tolbutamide treatment, total material and patients with abnormal IVGT Symbols as in Fig. 8.

The *mean relative heart volume* in the patients with SVEB atrial fibrillation and/or digitalis treatment during hospitalization was 508 ml/m² BSA, which was significantly greater than 435 ml/m² BSA of those without this characteristic ($P<0.001$) In the former category the corresponding volume of those who died was even greater 590 ml/m² BSA, and differed from 476 ml/m² BSA ($P<0.01$) of those surviving. The relative heart volume in these patients bore no relationship to VEB

In the tolbutamide group 7 patients experienced chest pain prior to death while in 4 this came suddenly information was not available about 2. These findings were not different from those in the control group The mean survival time of those who died after chest pain was 25 months compared with 8 in the control group ($P<0.01$) while the corresponding difference between those who died suddenly was not significant, i.e. 9 months compared with 3 months.

The corresponding mean survival times of the dead who had not had cardiac complications, major arrhythmias or VEB were significantly longer in the tolbutamide group than in the controls ($P<0.05$ in all instances) the figures ranging from 17—23 months and 3—5 months respectively On the other hand, the mean survival times

TABLE 27 Physical working capacity and relative heart volume in 47 patients during the follow-up in relation to IVGT

	IVGT	
	Abnormal	Normal
Total number	21	26
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Women	5	3
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Maximal pulse rate when in steady state	122	170
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[a]) n=23

[b]) Equivalent to *kilopond meter (kp m)*

groups. The characteristics and results are given in Table 27. At the time of the test 21 of them had abnormal IVGT and 26 normal IVGT. All were in sinus rhythm and 6 patients in each IVGT group were receiving digitalis treatment. No differences were observed between these 2 subgroups regarding physical working capacity which also was unrelated to tolbutamide treatment. These findings do not seem give support to the assumption by Ettinger et al. (1968) of a correlation between cardiac decompensation and abnormal IVGT.

TOLBUTAMIDE GROUP

RESULTS

As in the control group the overall survival was significantly lower in the patients with *SVEB* or *atrial fibrillation* ($P<0.001$) taken separately as well as after the addition of those who had received digitalis ($P<0.001$) as shown in Table 25. The one year survival rate for tolbutamide treated patients with *SVEB, atrial fibrillation and/or digitalis treatment* on the other hand was significantly higher i.e. 38 out of 43 or 86 per cent, than in the control group i.e. 31 out of 45 or 69 per cent ($P<0.05$) as illustrated in Fig. 12, and a total of 12 of the 13 dead patients had had this latter combination of clinical characteristics. Moreover in such patients observed for at least 24 months, 12 out of 27 controls, i.e. 44 per cent, died compared with 4 out of an equal number of tolbutamide-treated ones, i.e. 15 per cent ($P<0.05$).

Regarding the occurrence of *cardiac complications* there was no difference in total mortality between the tolbutamide treated patients and the controls, but over 18 months the survival rate was higher in the former group i.e. 55 out of 60 who survived compared with 35 out of 47 controls ($P<0.05$) (Fig. 11).

As seen in Table 25 and Figs. 8 and 10 the overall survival rate of the tolbutamide-treated patients was uninfluenced by *VEB* or *major arrhythmias* occurring during hospitalization in contrast to findings in the control group. Furthermore, in the patients with VEB the overall survival in the tolbutamide group was significantly better than in the control group ($P<0.05$) but not in those with major arrhythmias.

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The presence of SVEB atrial fibrillation and/or digitalis treatment implied a reduced chance of survival, i.e. 32 per cent, but during the first 12 months survival was better than in corresponding controls, as 27 out of 31 in the tolbutamide group survived compared with 18 out of 29 controls ($P<0.05$).

LONG-TERM TOLBUTAMIDE TREATMENT AND IVGT

INTRODUCTION

Individuals who exhibit signs of abnormal carbohydrate metabolism during ordinary or provoked glucose tolerance tests are prone to experience a progressive deterioration in carbohydrate control, as demonstrated by e.g. Fajans & Conn (1965) and O'Sullivan & Mahan (1968)

The primary aim of the present paper was to study the preventive effect of tolbutamide on myocardial reinfarction. At the same time this prompted further investigation into the influence of prolonged tolbutamide treatment on mildly impaired carbohydrate metabolism, as little information was available in the literature at the start of study (Fajans & Conn 1960 1962) Short-term administration of tolbutamide had been shown to improve IVGT (Lundbaek et al. 1959) Therefore the IVGT was followed by repeated testing throughout the study During its course further investigations on the effect of sulfonylurea treatment on asymptomatic diabetics have been published, but the results have been contradictory (Stowers et al. 1962, Stowers 1969 Keen 1966, Keen et al 1968, Belknap et al. 1967 Camerini Dávalos 1967 Feldman & Fitterer 1967)

Patients see also Chapter I.

Methods see also Chapter II.

As a rule the intravenous glucose tolerance test was repeated annually but for technical and other reasons this schedule could not always strictly be followed Thus led to an unbiased grouping of the patients according to the time lapse between their initial k value (k_o) and the k value of the retests. The mean of k values of the latter tests was therefore compared to the mean k_o of the group instead of that of the whole material in order to avoid a false difference. In the beginning of the study the first retest was performed after half a year but after some time this routine was abandoned In the 5 cases where the above mentioned retest was the only one performed, the k value obtained was considered as the last retest and used as such in the following calculations. The time elapsing between the first and the test thus ranged between 6—66 months, mean 2.8 years Patients in whom retests were performed after 4 or 5 years were grouped together for statistical purpose. In 15 of these latter patients belonging to the tolbutamide group yet another retest was performed one to 2 weeks later one hour after the ingestion of the morning dose of 0 5 g tolbutamide instead of after the routine discontinuation of the drug for 60 hours.

THE CONTROL GROUP

RESULTS

In this group of 83 patients, the k value underwent little change with time as shown in Table 28 and Fig 14. In the figure it is expressed in relation to the k_o of each group. It is seen that the range of the ratio lies between 0 99 and 1.01

In Table 28 and Fig. 14 the alterations of the k value in the patients with abnormal and normal IVGT were also analyzed separately In the former group the glucose tolerance improved temporarily i.e. the k value increased from 0.87 to 0 97 or 11 per cent during the first year, but this alteration was not significant. Thereafter it decreased stepwise, the decrease of the k-value being significant after 4—5 years, i.e from 0 94 to 0.82 or 13 per cent ($P<0\ 05$) In the group with normal IVGT the variations were not significant. Subgrouping according to age or obesity did not alter any of the findings in the control group

Three patients out of these 67 controls who completed the follow-up developed overt diabetes, i e. glucosuria and fasting capillary blood glucose exceeding 110 mg per 100 ml, which was detected

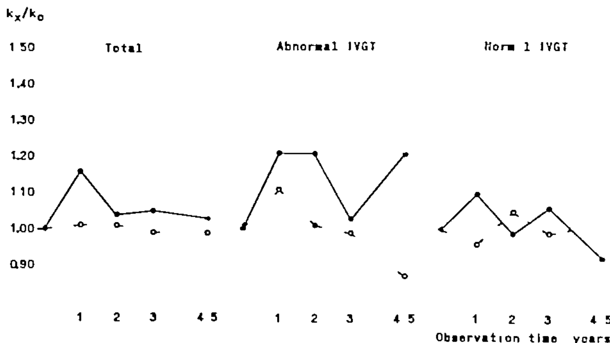


Fig. 14. Changes in the relation between k values obtained at repeated IVGTT (k_x) and k_o.
— control group ● — ● tolbutamide group. The point of the arrow indicates the ratio $\frac{k_{retest}}{k_{1-3}}$ (see Table 28)

3, 14 and 22 months after the myocardial infarction, respectively. Two of them were men, 57 and 60 years old, and one a woman, aged 79. Initially all had a diabetic k_o, range 0.75—0.80. As the mean observation time of the control group was 9 years, the incidence of diabetes mellitus was 3 out of 18 long-term survivors with diabetic IVGT or approximately 17 per cent within 3 years.

In 13 patients no retest was performed. In the remaining 70 no significant alteration of IVGT occurred, as measured by the last k value determined on an average 2.8 years after the infarction. The last IVGTTs did not differ from the initial ones. The means of k_o and the last k values were 1.16 and 1.12 respectively. Among those with diabetic, borderline, or normal k_o the corresponding means were 0.77—0.86, 1.01—1.00 and 1.47—1.34, respectively, as seen in Table 29.

In Table 30 IVGT is given in relation to prolonged treatment with diuretics (thiazides, chlortalidone or furosemide) and/or digitalis simultaneously with the research medication. No difference regarding the general observations ocurred, however, nor with regard to signs of heart failure during the hospital stay (p) having been present or absent.

The changes from the initial distribution of the k_o-values to that of the results of the last IVGTTs are illustrated in Fig. 15. Twelve out of 17 subjects (71 per cent) with borderline k_o had changed IVGT group as compared with 10 out of 33 (30 per cent) in those with alterations from normal k_o ($P<0.01$) while 8 out of 20 (40 per cent) changed in those with diabetic k_o. As a whole, only 8 out of 37 (22 per cent) patients with abnormal k_o had normal IVGT at last retest, however.

DISCUSSION

The IVGT in the entire control group before discharge from hospital underwent no significant change during the ensuing 4—5 years. This finding applies only to those with normal k_o. Those with abnormal k_o, in spite of initial improvement during the first year, subsequently deteriorated in IVGT. Three patients or 17 per cent of all long-

TABLE 28. Mean and ranges of k values in relation of repeated annual IV GTT and tolbutamide treatment

Retest		Total: No of patients	Total: Mean	Total: k_x/k_o	Total: Range	Total: P	Initial IVGT Abnormal: No of patients	Abnormal: Mean	Abnormal: k_x/k_o	Abnormal: Range	Abnormal: P	Initial IVGT Normal: No. of patients	Normal: Mean	Normal: k_x/k_o	Normal: Range	Normal: P
Control																
1 yr	k_o	65	1.18	1.01	0.59—2.79	N.S.	33	0.87	1.11	0.59—1.09	N.S.	32	1.48	0.96	1.12—2.70	N.S.
	k_1		1.19		0.58—3.00			0.97		0.58—1.48			1.42		0.74—3.00	
2 yrs	k_o	27	1.04	1.01	0.59—1.69	N.S.	17	0.89	1.01	0.59—1.06	N.S.	10	1.31	1.05	1.1—1.69	N.S.
	k_2		1.05		0.38—1.50			0.90		0.38—1.25			1.37		1.14—1.50	
3 yrs	k_o	40	1.13	0.99	0.69—2.17	N.S.	23	0.92	0.99	0.69—1.08	N.S.	17	1.42	0.99	1.14—2.17	N.S.
	k_3		1.12		0.57—2.61			0.91		0.57—1.63			1.40		0.87—[illegible]61	
4—5 yrs	k_o	18	1.17	0.99	0.76—2.17	N.S.	9	0.95	0.87	0.76—1.05	<0.05	9	1.41	1.02	1.12—2.17	N.S.
	$k_{4\text{-}5}$		1.16		0.74—2.61			0.82		0.74—1.29			1.44		0.78—2.64	
Tolbutamide																
1 yr	k_o	85	1.16	1.16	0.66—2.27	N.S.	46	0.91	1.21	0.66—1.08	<0.01	39	1.45	1.10	1.12—2.27	N.S.
	k_1		1.31		0.65—3.47			1.10		0.65—[illegible]84			1.60		0.64—3.47	
2 yrs	k_o	37	1.17	1.04	0.66—2.27	N.S.	20	0.92	1.21	0.66—1.07	<0.05	17	1.46	0.99	1.16—2.27	N.S.
	k_2		1.22		0.67—2.77			1.11		0.67—2.36			1.44		0.87—2.77	
3 yrs	k_o	37	1.24	1.05	0.80—2.27	N.S.	16	0.93	1.03	0.80—1.08	N.S.	21	1.46	1.06	1.16—2.27	N.S.
	k_3		1.30		0.70—3.47			0.96		0.73—1.8			1.55		0.70—3.47	
4—5 yrs	k_o	15	1.19*		0.80—1.61		7	0.95		0.80—1.07		8	1.41		1.18—1.61	
	$k_{4\text{-}5}$		1.23	1.03	0.63—2.05	N.S.		1.15	1.21	0.65—1.85	N.S.		1.30	0.92	0.70—2.03	N.S.
	$k_{4\text{-}5m}$		1.67*	1.36	0.86—3.46	<0.05		1.42*	1.23	0.86—2.41	<0.05		1.90	1.46	1.00—3.46	N.S.

k_o = value of Initial IVGTT (research medication discontinued 60 hours before test)
k_x = k value of repeated IVGTT (research medication discontinued 60 hours before test)
k_{xm} = k value of repeated IVGTT (research medication not discontinued before tests)

*) $\frac{k_{4\text{-}5m}}{k_o} = 1.40$ $P<0.05$ *) $\frac{k_{4\text{-}5m}}{k_o} = 1.49$ $P<0.05$

TABLE 30 Mean and range of k value in relation to k value of the first annual and last IV GTT and tolbutamide treatment

	Initial IVGT: Diabetic: No. of patients	Diabetic: Mean	Diabetic: $\frac{k}{k_0}$	Diabetic: Range	Diabetic: P	Borderline: No. of patients	Borderline: Mean	Borderline: $\frac{k_1}{k_0}$	Borderline: Range	Borderline: P	Normal: No. of patients	Normal: Mean	Normal: $\frac{k}{k_0}$	Normal: Range	Normal: P	Total: No. of patients	Total: Mean	Total: $\frac{k}{k_0}$	Total: Range	Total: P
Control																				
k_0	17	0.78	1.15	0.39—0.89	N.S.	16	1.01	1.04	0.92—1.09	N.S.	3	1.48	0.96	1.12—2.70	N.S.	63	1.18	1.01	0.39—2.70	N.S.
k		0.90		0.38—1.48			1.05		0.78—1.44			1.42		0.74—3.66			1.19		0.38—3.00	
k_0	20	0.77	1.12*	0.39—0.89	N.S.	17	1.01	0.99	0.92—1.09	N.S.	33	1.47	0.91	1.12—2.70	N.S.	70	1.16	0.97	0.39—2.70	N.S.
k_L		0.86		0.46—1.25			1.00		0.78—1.37			1.34		0.78—2.69			1.12		0.16—2.69	
Tolbutamid																				
k_0	20	0.81	1.41	0.66—0.89	<0.01	26	0.99	1.07	0.91—1.08	N.S.	39	1.43	1.10	1.12—2.27	N.S.	85	1.16	1.16	0.66—2.27	<0.05
k_1		1.14		0.67—2.84			1.06		0.65—1.88			1.60		0.68—3.47			1.34		0.67—3.47	
k_0	21	0.81	1.43	0.66—0.89	<0.01	29	0.99	1.13	0.91—1.08	N.S.	40	1.43	1.01	1.12—2.27	N.S.	90	1.14	1.11	0.66—2.27	=0.01
k_L		1.16		0.73—2.84			1.12		0.63—1.83			1.44		0.73—2.77			1.27		0.73—2.84	

k_0—k value of initial IVGTT
k_1—k-value at retest after one year
k_L=k-value of last IVGTT

) $P<0.05$
) $P<0.01$

TABLE 10 Mean k [illegible] in relation to the last k-value during long-term diuretic or digitalis therapy and tolbutamide treatment

Initial IVGT

		Diabetic				Borderline				Normal				Total			
		No of patients	Mean	k_L/k_o	P	No of patients	Mean	k_L/k_o	P	No. of patients	Mean	k_L/k_o	P	No. of patients	Mean	k_L/k_o	P
Control																	
Diuretics	k_o	7	0. 6	1.08	N.S.	9	1.01	0.94	N.S.	7	1.24	1.06	N.S.	23	1.00	1.02	N.S.
	k_L		0.82				0.95				1.31				1.02		
No diuretics	k_o	13	0.78	1.14	N.S.	[illegible]	1.0	1.04	N.S.	6	1.53	0.91	N.S.	47	1.23	[illegible]	N.S.
	k_L		0.89				1.06				1.39				1.12		
Digitalis	k_o	11	0. 4	1.08	N.S.	5	1.03	0.93	N.S.	[illegible]	1.42	1.01	N.S.	24	1.02	1.03	N.S.
	k_L		0.80				0.96				1.44				1.05		
No digitalis	k_o	[illegible]	0.82	1.13	N.S.	[illegible]	1.01	1.00	N.S.	[illegible]	1.49	0.91	N.S.	[illegible]	1.23	[illegible]	N.S.
	k_L		0.93				1.01				1.35				1.18		
Tolbutamide																	
Diuretics	k_o	[illegible]	0.80	1.28	<0.01	[illegible]	1.00	1.06	N.S.	11	1.50	[illegible]	N.S.	32	1.11	[illegible]	S.
	k_L		[illegible]				1.06				1.19				[illegible]		
No diuretics	k_o	[illegible]	[illegible]	1.55	<0.05	17	0.99	1.17	N.S.	[illegible]	1.43	1.08	N.S.	[illegible]	1.18	1.16	S.
	k_L		[illegible]				1.16				1.54				1.37		
Digitalis	k_o	[illegible]	0.51	1.26	<0.01	[illegible]	1.00	1.1	N.S.	[illegible]	1.55	[illegible]	N.S.	[illegible]	1.09	1.10	S.
	k_L		[illegible]				1.1				1.42				1.29		
No digitalis	k_o	[illegible]	0.81	1.54	<0.01	17	0.99	1.09	N.S.	[illegible]	1.43	1.01	N.S.	[illegible]	1.18	1.11	S.
	k_L		1.25				1.08				1.45				1.31		

k_o — k-value of [illegible] IVGTT
k_L — k-value of last IVGTT

term survivors with initially diabetic IVGT developed overt diabetes. Among patients with borderline or normal IVGT no such decompensation of glucose tolerance was observed.

Few follow-up studies of glucose tolerance after an acute myocardial infarction have been published. Goldberger et al. (1945) reported a rapid deterioration of oral glucose tolerance after the acute illness. They observed that although 7 out of 11 patients had a normal OGT after the attack, 5 of them progressively exhibited diabetic OGTTs over a period extending to 13 months, while in one case the initially abnormal glucose tolerance became normal.

Eckerström (1951) arrived at a different result when reexamining 12 patients 4—11 years after myocardial infarction. They constituted those survivors who could be traced out of 242 patients, of whom 223 were known to have died. All but one of these 12 cases had a normal OGT irrespective of their having had hyper- or normoglycemia during the acute illness.

Likewise the follow-up studies by Sowton (1962) and Datey & Nanda (1967) indicated a progressive improvement in the OGT. Sowton (1962) found that 43 per cent of 30 patients had abnormal OGTTs 6 months after the myocardial infarction as compared with 73 per cent immediately after it. The alteration in 13 patients followed for at least 3 years was from 62 per cent abnormal OGTTs in the acute phase to 30 per cent by the time of the follow-up. Datey & Nanda (1967) stated the corresponding rate after one to 2 years to be 31 per cent in 54 patients, while it was 47 per cent one month after the acute episode in 145 out of 167 consecutive patients with acute myocardial infarction.

The only follow-up study of the IVGT after myocardial infarction has been published by Wahlberg (1966) who retested 74, 65 and 42 patients within 6 months, 7 to 24 months, and more than 24 months, respectively, after the acute attack. The difference between the means of the initial k values and those of the retests performed in the above intervals did not exceed 0.05 in any instance. The frequency of abnormal IVGTTs ranged between 55—67 per cent. At the last retest in 129 out of 190 survivors from a first acute myocardial infarction over a period extending to 5 years 6 per cent had abnormal glucose tolerance. Initially 60 per cent of the patients had an abnormal IVGT.

The latter findings are in agreement with those in the control group though it must be remembered that a small number of the subjects in the present study were also included in that of Wahlberg's.

No epidemiological data on the natural course of glucose tolerance in the general population have been published, but 2 studies of selected groups have been issued. Wilansky & Hahn (1967) reported on the course of latent diabetes, characterized by a positive cortisone OGTT in relatives of diabetics. In 20 patients observed for 3 years complete remission ocurred in 10 per cent, while in 40 per cent overt diabetes emerged. The corresponding incidences were similar also in a more recent report (Wilansky & Shochat 1968). O'Sullivan & Mahan (1968) performed annual OGTTs in 1013 nonpregnant women aged 19—50 years. According to diagnostic criteria for chemical diabetes of Mosenthal & Berry, Fajans & Conn, or US Publ. Health Service (see their Table I) 352, 263 or 159 subjects, respectively, had such diabetes. The 3-year incidence of clinical diabetes mellitus can be calculated from their figure to be 5, 6 and 18 per cent, respectively. Although the incidence in the latter study according to the criteria of the US Publ. Health Service agrees with the corresponding incidence in patients with diabetic IVGT of the present study, the varying test methods and samples studied render impossible any conclusion about the corresponding incidence in a general population.

Keen et al. (1968) reported that no systemic difference was observed in the mean 2 hour blood sugar behaviour in control subjects with borderline OGT as compared with tolbutamide treated ones during a 5-year follow-up. This might be interpreted as no decompensation occurring to overt diabetes in their 248 subjects with borderline OGT, but unfortunately no specific information is given in this respect. Three patients out of 190 first myocardial infarctions studied by Wahlberg

(1966) developed clinical diabetes within 2.5 years. As these patients were not controlled regularly the true incidence could have been higher

Treatment with diuretics has been observed to provoke hyperglycemia in some non-diabetic patients (Shapiro et al. 1961 Breckenridge et al. 1967) In the present study there seemed to be a consistent tendency to somewhat lower IVGT at the last retests in patients treated with diuretics, but no differences were significant. These findings are in accordance with those given by Wahlberg (1966) though he made reservations about the duration of diuretic treatment which lasted in many of the patients for a short time. In the present series this treatment had lasted for years in most of these patients, which indicates that the hyperglycemic effect of diuretics is a mild one even after long-term administration. This finding agrees also with that of Jackson & Nellen (1966)

The indication for treatment with diuretics may have been hypertension and/or heart failure. In order to evaluate the influence of the latter factor prolonged digitalis treatment was related to IVGT since patients on this drug most probaly had had symptoms of heart failure, because at each control visit the indications for continued medication were reconsidered Patients presenting SVEB, atrial fibrillation and/or digitalis treatment indicating (p 52) heart failure during their hospital stay did not differ in this respect from those without signs of heart failure. Patients on diuretics as those with these signs showed a less marked improvement of IVGT in comparison with the initial IVGT but again without significance. Thus, it seems as if in long-term survivors presenting with heart failure IVGT was not adversely influenced

THE TOLBUTAMIDE GROUP

RESULTS

During the first year the mean k value improved significantly from an initial 1 16 to 1 34, i.e. a 16 per cent change ($P<0.05$) After 2 years the improvement had declined to 8 per cent, and to 5 per cent at retests performed 3 and 4—5 years after the myocardial infarction, the differences not being significant (see Table 28 and Fig. 14) but the results of the last retest in 90 patients, on an average 2.8 years after the myocardial infarction, showed a significant overall improvement of the mean k value from 1 14 to 1.27 ($P=0\,01$) as shown in Table 29

A separate study of the 3 IVGT groups showed that in the patients with a diabetic k_e the mean k value increased from 0.81 to 1 14, i.e. to normal IVGT during the first year ($P<0.01$) The corresponding alterations in the subjects with borderline or normal k_e values were insignificant, i.e. 0 99—1.06 and 1 45—1 60 respectively (Table 29) In the patients with abnormal IVGT initially the corresponding improvement was from 0 91 to 1 10 or 21 per cent ($P<0.01$) and still after 2 years the amelioration was of the same order i.e. 0 92—1 11 ($P<0\,05$)

The last retest yielded similar improvement of the k values in subjects with diabetic k_e, the change being from 0.81 to 1 16 ($P<0\,01$) those in the 2 other IVGT groups being insignificant, i.e. 0 99—1 12 and 1 43—1 44 respectively (Table 29) The mean k value of all patients with abnormal IVGT initially increased from 0.91 to 1 14 ($P<0\,01$)

The above significant alterations of IVGT were neither correlated to age nor to obesity Subgrouping according to prolonged treatment with diuretics (thiazides, chlortalidone, or furosemide) and/or digitalis did not alter the overall improvement of IVGT by tolbutamide treatment observed in patients with initially diabetic IVGT of the total series, as illustrated in Table 30 This was also irrespective of whether signs of heart failure had occurred or not during hospitalization. The corresponding improvements were also significant with regard to all patients with abnormal IVGT In subjects with initially normal IVGT an insignificant lowering of the IVGT occurred in contrast to those not receiving diuretics and/or digitalis.

In Fig. 15 the distribution of the last k values are given in relation to the initial IVGT grouping The percentages remaining unaltered in the diabetic and borderline IVGT groups, i.e. 38 and 28

term survivors with initially diabetic IVGT developed overt diabetes. Among patients with borderline or normal IVGT no such decompensation of glucose tolerance was observed.

Few follow-up studies of glucose tolerance after an acute myocardial infarction have been published. Goldberger et al. (1945) reported a rapid deterioration of oral glucose tolerance after the acute illness. They observed that although 7 out of 11 patients had a normal OGT after the attack, 5 of them progressively exhibited diabetic OGTTs over a period extending to 13 months, while in one case the initially abnormal glucose tolerance became normal.

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differences. Solely in patients with initially diabetic IVGT the mean k value after one year and at the last retest were significantly higher in the tolbutamide group than in those of the control group ($P<0.01$ in both instances). In the former group the last k value had increased from 0.81 to 1.14 as compared with 0.77 to 0.86 in the latter group. The corresponding changes of the fasting blood sugar values were 82 to 84 mg per 100 ml in the tolbutamide group and 85 to 87 mg per 100 ml in the control group, no differences being significant.

As seen in Fig. 15 and mentioned previously 22 per cent controls with initially abnormal IVGT had normalized this at the last retest compared with corresponding 46 per cent in the tolbutamide treated patients ($P<0.05$). In those with normal k, similar proportions had deteriorated, i.e. 33 and 25 per cent, respectively.

The mean k value of the retests performed without stopping tolbutamide medication was higher than that of the controls after 4—5 years, or 1.67 as compared with 1.16 ($P<0.05$).

DISCUSSION

From the repeated IVGTTs one might conclude that long-term tolbutamide treatment induced a significant amelioration of glucose tolerance in patients with abnormal IVGT over a period extending to nearly 3 years. This was found if this drug had been discontinued for 60 hours before retesting. During uninterrupted tolbutamide therapy corresponding improvement in IVGT was observed for as long as 4—5 years, i.e. under the same conditions that were valid for the tolbutamide treated patients during the trial. No studies of the effect of antidiabetic treatment on survivors from myocardial infarction without overt diabetes have been reported, but in a number of papers the effects of prolonged sulfonylurea treatment has been described in subjects with asymptomatic diabetes. Fajans & Conn (1960) treated 19 patients with asymptomatic diabetes mellitus, aged 11—35 years, for 15 to 52 months with tolbutamide. At retest after discontinuation of this drug for 12 hours, 10 were normal, 6 improved, and 3 unimproved. In 9 subjects aged 37 to 49 with the same or lesser degree of abnormality only 2 improved after 24 to 49 months of treatment.

Similar observations have been reported with chlorpropamide treatment in patients with abnormal IVGT but without symptoms of overt diabetes (Stowers et al. 1962, Stowers 1969). In the latter report it was stated that IVGT had improved significantly after a mean treatment time of 20 months. The retests were performed 3 weeks after temporary discontinuation of the drug. The effect of treatment is difficult to evaluate as both these studies lacked a control group and spontaneous remissions to normal have been noticed in nearly 40 per cent of patients with early diabetes during one to 2 years after the diagnosis (O'Sullivan & Hurwitz 1966).

In the literature 5 controlled trials have been reported of tolbutamide treatment in subjects described as asymptomatic diabetics or as having abnormal glucose tolerance. Though the patient materials and the glucose tolerance test methods may not be quite comparable, a review of these studies is of interest. A summary is presented in Table 31.

Treatment with one gram tolbutamide daily over a period extending one year or more resulted in improvement of glucose tolerance in 3 of the studies, while no alteration was observed in 2.

Engelhardt & Vecchio (1965) consistently noticed lower 30 and 60 minutes values during repeated short OGTTs during 8—24 months periods of treatment with tolbutamide in 20 patients as compared with 22 controls (mean ages 46 to 48), the averages of these values being statistically significant. They noticed only a lowering of the post-treatment fasting blood glucose values but not of OGTT. Medication was withheld on the morning of the test.

Belknap et al. (1967) conducted a double-blind cross-over study for 2 years in 34 men (mean age 57, range 33—75 years) (also described in Chapter VII). IVGT improved significantly. Treatment was omitted in the morning prior to the retest. Feldman & Fitterer (1967) registered a consistently increasing proportion of improved or normal OGTTs after 4, 8 and 12 months of tolbutamide

TABLE 31 Long-term tolbutamide treatment of subjects [illegible] results from 5 controlled trials and the present study

	Initial glucose tolerance	No. of subjects		Mean age (Range)	Treatment time, months	Glucose tolerance	
		Tolbutamide	Control			Improved	Treatment discontinued
Engelhardt & Vecchio (1965)		20	—	47	14	yes	12 hrs
Belknap et al. (1967)	c	54	54	57	1	yes	12 hrs
Camerini-Dávalos (1967)	b c	38	59	34	10—4	no	72 hrs
Feldman & Fitterer (1967)	a	45	26	(15—39)	12	yes	3 days
Keen et al. (1968)		126	1[illegible]2	50 (?)	60	no	10 days
Present study		53	48	60	1—66	yes 1—2 yrs	60 hrs
	d	42	35	57	12—66	no	60 hrs

) abnormal OGT) abnormal cortisone OGT °) abnormal IVGT) normal IVGT °) cross-over

treatment, while glucose tolerance decreased gradually in a control group. The alteration was statistically significant, however, only in non-obese subjects, aged 40—49. Tolbutamide was discontinued for 3 days prior to the test.

Camerini-Dávalos (1967) found no difference in improvement or impairment of OGT after 10 months to 2 years, whether the 97 subjects studied (34 years, range 15—44) had received tolbutamide or placebo. Medication was withheld for 72 hours.

Finally, Keen et al. (Keen 1966, Keen et al. 1968) could not observe any permanent or temporary change of 2 hour glucose values at repeated OGTTs over a 5-year period in those of 248 subjects (mean age approximately 55 estimated from their Fig. 1—2) who were treated with tolbutamide. Medication was discontinued for 10 days prior to the retests except for once when it was continued up to and including the day of the clinic visit, but in spite of continued tolbutamide treatment, the blood sugar response was not lower than that of the control patients, as might have been expected.

Hence, most studies suggest the time of discontinuation of tolbutamide treatment to be of importance with regard to possible influence upon glucose tolerance. In the 2 former investigations discussed above it was withheld only on the morning of the test, while in the latter two except for that of Keen et al. that showed no effect, the discontinuation ranged from 3 to 10 days. However, the improvement in glucose tolerance registered by Feldman & Fitterer (1967), though significant in a subgroup only, was still present after discontinuation of tolbutamide for 72 hours. Camerini-Dávalos (1967), using the same technique, found no improvement of OGT. As a corresponding subgroup was not studied by Camerini-Dávalos, comparisons in this respect cannot be made.

In the present study the time of discontinuation of tolbutamide was 60 hours, corresponding to that of Camerini-Dávalos (1967). But contrary to his findings, significant improvement of glucose tolerance over 2 years was observed in patients with abnormal glucose tolerance. The discrepancy in this respect is not readily apparent, though different test methods may contribute to the dissimilarity.

The failure of tolbutamide to induce improvement in glucose tolerance during any phase of the follow-up in Bedford by Keen et al. (1968) in

contrast to the constant amelioration observed in the present study cannot only be attributed to their longer time of discontinuation of tolbutamide i. e. 10 days as compared with 60 hours, because in both studies the concentration of circulating tolbutamide at retests should have been negligible (Stowers et al. 1958). Yet in patients with maturity-onset of overt diabetes, sulfonylurea induced amelioration of glucose tolerance is often observed to deteriorate if the treatment is discontinued (Singer & Hurwitz 1967, Fajans & Conn 1965). Sheldon et al. (1966) observed that an improvement brought about by acetohexamide remained essentially unaltered 3 weeks after the withdrawal of treatment in 13 subjects with diabetes of short duration. Stowers (1969) reported that prolonged chlorpropamide treatment improved IVGT which continued for 3 weeks after stopping therapy and was present still one year later, in 2 thirds of a selected group of good responders. Unfortunately no control group was followed simultaneously and spontaneous remission is not rare in early diabetes mellitus (O'Sullivan & Hurwitz 1966).

The implications of the different principles of selection between the present patient series and that of Keen et al. (1968) is difficult to evaluate in this respect. The former comprises only patients with obvious manifestation of atherosclerosis, while in the latter borderline glucose tolerance in individuals of a general population has been the indication for participation.

Fajans & Conn (1965) and Stowers (1969) stated that tolbutamide brought about improvement more often in younger age groups with mild glucose intolerance than in older, though Feldman & Fitterer (1967) found the reverse. In the present study group age did not influence the response to treatment. The best effect of tolbutamide in the investigation of the latter was observed in the non-obese, but this factor also was without importance in the present study.

It has been suggested that the improvement induced by sulfonylurea therapy in patients with mild diabetes may depend primarily on the maintenance of lower glucose levels (Sheldon et al. 1966). In the present series no differences in fasting blood sugar values were seen in these subjects with diabetic IVGT initially in whom an improvement was observerd.

Simultaneous prolonged treatment with diuretics and/or digitalis did not influence the improvement in IVGT observed in the present series in subjects with abnormal or diabetic IVGT initially in contrast to observations by others in non-diabetic subjects (Shapiro et al. 1961, Breckenridge et al. 196). A deterioration tendend to occur in patients with normal IVGT, though insignificant both a concomitant treatment with diuretics or digitalis, this differing tendency in relation to IVGT being difficult to assess. Finally, signs indicating heart failure during the acute episode, which in Chapter V were shown to imply an adverse prognosis indicated no tendency to differ from others as regards future IVGT changes.

Tolbutamide is considered to act through stimulation of synthesis and release of endogenous insulin. Abnormally high insulin responses to glucose loading have been found in patients with coronary heart disease (e.g. Nikkilä et al. 1965, Peters & Hales 1967). On the other hand, a comparison between the insulin response to hyperglycemia in different subjetcs must be related to its stimulus, as stressed by Cerasi & Luft (1967) and Seltzer et al. (1967). Mahler (1966) has suggested that through the inhibitory effect of insulin on tissue lipase the formation of lipids in the arterial wall is increased. Experimental animal investigation has furthered this hypotesis (Stout 1968, Stout & Vallance-Owen 1969). The results of the present clinical follow-up in survivors from myocardial infarction study do not support this hypotheses.

Knowledge of the relationship between insulin response, IVGT and the actual concentration of circulating tolbutamide during IVGTT would be of interest. This is at present under investigation.

CONCLUSIONS

The IVGT of the control group as a whole underwent no significant change during the 4—5 study years. However, those with abnormal k_g, in

spite of initial improvement during the first year subsequently deteriorated in IVGT

Long term tolbutamide treatment induced a significant amelioration of glucose tolerance in patients with abnormal IVGT over a period extending to nearly 3 years. This was found if this drug had been discontinued for 60 hours before retesting. During uninterrupted tolbutamide therapy corresponding improvement in IVGT was observed for as long as 4—5 years.

Prolonged diuretic therapy or heart failure appeared not to influence the above findings.

LONG-TERM TOLBUTAMIDE TREATMENT AND SERUM LIPIDS

INTRODUCTION

An association between high serum levels of cholesterol and triglycerides and coronary heart disease has been clinically and epidemiologically proven. This has prompted investigations of dietary and non-dietary methods of controlling hyperlipoproteinemia after myocardial infarction in the hope of reducing the risk of recurrences. The results of a number of trials are still inconclusive, however as has been dicussed in Chapter IV The effect of tolbutamide on circulating serum lipids is controversial. When during the course of the present trial tolbutamide was found to influence long-term survival after myocardial infarction, an investigation of the serum lipids was considered to be of interest. Besides, since a significant difference had also been found between serum lipid levels in patients of the present study and those in matched controls (to be published) an evaluation of the drug in this respect was further considered desirable. In order to diminish the influence of temporary or seasonal variations each patient was studied for one year (Tibblin & Cramér 1963 Carlson & Lindstedt 1969)

Patients see also Chapter I

Methods see also Chapter II

During the trial, sera from fasting patients were routinely taken at the time of discharge from hospital. To fulfill the purpose of this particular retrospective study sera from 46 patients were available. Eighteen of these had received a placebo and 28 tolbutamide. Six in the former group and 4 in the latter were women. For mode of treatment and dietary recommendations, see Chapter II. The mean ages and the intravenous glucose tolerance are given in Tables 32 and 33

RESULTS

The serum cholesterol values were essentially the same in the 2 treatment groups both at the start of the trial and one year later (Table 32) No relation between serum cholesterol and IVGT was found.

There was no difference in serum triglyceride levels between the groups before treatment, but after one year a significant decrease was observed in the tolbutamide-treated group ($P<0.01$) while an insignificant increase occurred in the control group as shown in Table 32 and Fig. 16. The same pattern was evident for men in the tolbutamide treatment group ($P<0.01$) the women being too few for a corresponding analysis After one

TABLE 32 Mean ages at the time of myocardial infarction alteration in means and range of weight k-values and serum cholesterol level after one year' tolbutamide treatment

	Control (n=18)					Tolbutamide (n=28)				
	Before		After			Before		After		
	Mean	Range	Mean	Range	P	Mean	Range	Mean	Range	P
Age, years	59	39—79				57	41—69			
Weight, kg	72	53—90	73	51—90	N.S.	76	50—102	74	47—98	N.S.
k value	1.15	0.59—1.85	1.18	0.38—1.88	N.S.	1.07	47—98	1.28	0.64—2.84	<0.01
Cholesterol, mg per 100 ml	249	180—396	255	160—425	N.S.	254	160—350	256	170—440	N.S.

TABLE 33 Alterations in mean and ranges of serum triglyceride levels (mmole/liter) after one year's tolbutamide treatment in relation to initial level IVGT and sex

	Control						Tolbutamide					
	No. of	Before		After			No. of	Before		After		
	patients	Mean	Range	Mean	Range	*P*	patients	Mean	Range	Mean	Range	*P*
Total	18	2.18	1.07—3.30	2.50[a]	1.01—7.50	N.S.	28	2.30	1.32—6.90	1.86[a]	0.95—6.50	N.S.
Abnormal IVGT	10	1.99	1.07—2.94	2.85	1.32—7.50	N.S.	17	2.41	1.32—6.90	1.88	0.95—6.50	<0.01
Normal	8	2.41	1.77—3.30	2.04	1.01—3.56	N.S.	11	2.13	1.40—2.85	1.63	1.30—2.30	N.S.
Men	12	2.13	1.07—3.30	2.00	1.01—2.68	N.S.	24	2.15	1.40—3.30	1.70	0.95—3.25	<0.01
Initial triglyceride level												
≤2.00	8	1.63	1.07—1.96	1.99	1.32—2.42	N.S.	14	1.73	1.32—2.00	1.41	1.00—2.08	<0.01
>2.00	10	2.63	2.11—3.30	2.90	1.01—7.50	N.S.	14	2.88	2.10—6.90	2.19	0.95—6.50	<0.01

) $P<0.05$) $P=0.01$

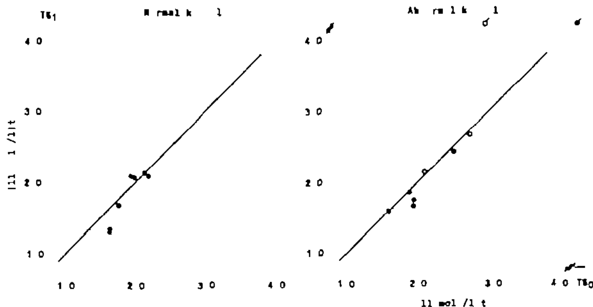


Fig 16. Serum triglyceride values in relation to k_g after one year's follow-up control group ● tolbutamide group TG_0 initial value TG_1 after one year. The 2 uppermost symbols denote excess values: see text.

year's treatment the difference between the serum triglyceride values in the 2 groups was significant ($P<0.05$)

No relation between the serum triglyceride values and IVGT before the start of the trial could be observed

In Table 33 the treatment is also considered in relation to the serum triglycerides and IVGT. In the control group triglycerides increased among patients with abnormal and decreased among those with normal glucose tolerance, although not significantly. While the lowering of these values was significant in tolbutamide-treated patients with abnormal IVGT ($P<0.01$) the change among those with normal IVGT was less. This is also illustrated in Fig 16. The post-treatment values of the 2 groups with abnormal IVGT differed significantly ($P=0.01$) as they did when only men were considered

Obesity was unassociated with serum triglyceride level and the effect of treatment. Tolbutamide lowered serum triglycerides irrespective of the initial serum levels, as illustrated in Table 33

As seen in the same table the IVGT improved significantly with treatment ($P<0.01$)

The body weight increased from 73 to 77 kg in controls with normal glucose tolerance ($P<0.05$) but no other significant differences of body weight could be observed between or within the treatment groups at the start of the trial, nor one year later (Table 32)

DISCUSSION

The results of a study in non-diabetic survivors from a myocardial infarction of the effect of tolbutamide on serum lipids suggested a significant reduction of serum triglycerides in those with abnormal IVGT. No influence upon serum cholesterol values was detected. This dissimilarity might partially be due to the fact that the mean triglyceride level was higher than that of the normal population in Stockholm, while cholesterol levels were more alike (Carlson & Lindstedt 1969). The IVGT was significantly improved by tolbutamide treatment. Serum cholesterol and triglyceride values in subjects with normal IVGT underwent no significant alteration, though a spontaneous decrease of 25 per cent of the latter was noticed in these controls simultaneously with a significant increase in weight.

One female patient in each treatment group (both with diabetic IVGT) exhibited excessive serum triglyceride levels. The values before and after the observation period were 2.94—7.50 and 6.90—6.50 mmole/liter respectively, the latter pair of values found in the tolbutamide treated patient. If these subjects are excluded the differences between the means presented in Table 33 will decrease. The mean serum triglyceride levels before treatment in the controls and tolbutamide treatment groups would then be 2.13 and 2.14 mmole/liter respectively and 2.30 and 1.69 mmole/liter after treatment, respectively. The above statistical differences remained unaltered.

Sulfonylurea therapy has been observed to lower circulating triglyceride levels, in patients with mild stable diabetes (Carlson & Östman 1961, Morris et al. 1964, Farquhar et al. 1966) while serum cholesterol values were uninfluenced when investigated.

However Belknap et al. (1967) arrived at a contradictory result in a careful double-blind study of tolbutamide treatment for one year on a group of male patients with abnormal IVGT (except for one subject with normal IVGT but pathological oral glucose tolerance). No effect on plasma triglyceride levels were found. In comparison with those patients of the present study with abnormal IVGT in whom a lowering of the serum triglyceride levels was observed, no differences are apparent among the subjects studied by Belknap et al. as to age, body weight, degree of glucose impairment, duration and dose of tolbutamide treatment. In the present study all the patients had suffered from a myocardial infarction. In contrast, in the study by Belknap et al. the patients only exhibited a mild impairment of glucose tolerance. To what degree this difference in the materials is responsible for the d vergi g results is difficult to assess.

Camerini Dávalos (1967) observed a significant increase of the serum triglycerides after 10—24 months of tolbutamide treatment in 25 subjects with chemical diabetes, i.e. 3 abnormal standard or cortisone primed oral glucose tolerance tests or IVGTTs. The differing numbers of patients tested before and after treatment suggest that all the values did not belong to the same subjects. The corresponding findings in the placebo group are not given.

Belknap et al. (1967) could not notice any specific influence of tolbutamide on abnormal lipid values. In the present study the change was somewhat greater, or 24 per cent, in those with initial serum triglyceride levels of more than 200 mmole/liter as compared with 18 per cent in those with lower values. The reduction was significant at both levels, however ($P < 0.01$ in both instances).

Belknap et al. (1967) found a significant improvement of IVGT by tolbutamide treatment, which agrees with the results of the present study.

Contrary to the observations by Albrink & Davidson (1966) but in agreement with others (Herman & Gorlin 1964, Carlson & Wahlberg 1966, Nikkilä et al. 1965, Belknap et al. 1967, Christiansen et al. 1968, Henle et al. 1969) the serum cholesterol and triglyceride levels were not correlated to IVGT.

Weight loss has been held responsible for an observed decrease of serum triglycerides (Porte et al. 1966, Levy & Glueck 1969). The patients with abnormal IVGT in the tolbutamide treatment group did lose weight, but this must be considered in relation to the weight losses of corresponding controls with concomitant increase of serum triglyceride values or the reverse findings in those with normal IVGT. Furthermore only this latter weight increase was significant.

CONCLUSION

The clinical significance of the serum triglyceride lowering effect of tolbutamide in survivors from a myocardial infarction is difficult to assess. It is noteworthy, however, that the benefit of tolbutamide treatment both regarding survival and serum triglyceride levels was observed in the same patient group, namely the one with abnormal gl cose tolerance.

SUMMARY AND CONCLUSION

I Clinical and epidemiological studies have established an association between clinically manifest atherosclerotic vascular disease and impaired glucose tolerance. In survivors from a first myocardial infarction without overt diabetes mellitus the *intravenous glucose tolerance (IVGT)* has been shown to be abnormal 4 times the rate found in controls, and, furthermore, their long-term survival is adversely affected by abnormal IVGT. These observations prompted a study of antidiabetic drug treatment in such patients.

II The aim of the present investigation was to study the effect of long-term tolbutamide treatment primarily on the prognosis but also on other manifestations of cardiovascular disease and IVGT in survivors from a first myocardial infarction without overt diabetes mellitus.

III. From January 1963 through 1967 a total of *270 survivors from a first acute myocardial infarction* were discharged from the Department of Medicine at Serafimerlasarettet, Stockholm. Ninety two were excluded from the trial mainly because of history or signs of overt diabetes or other disease known to interfere with carbohydrate metabolism, domicile outside the Stockholm area or refusal to participate. Hence, the *study group comprised 178 patients* mean age 59 years. There were *145 men* mean age 58 years, and *33 women* mean age 68 years.

IV The IVGT was tested with a single load of 25 g of glucose injected in 2—4 minutes. Using the formula $0.696 \times 100/t_{\frac{1}{2}}$ the result of the test was expressed as a *k value* representing the per cent per minute reduction of blood glucose. This test has been used at Serafimerlasarettet since 1960 and found to have good reproducibility suitable for a follow-up study. *k values* exceeding 1.10 were classified as *normal* and others as *abnormal* which were subdivided into *borderline* (0.91 to 1.10) and *diabetic* (0.90 and lower).

V The mean k value of the total series was 1.14. Twenty-nine per cent had a diabetic, 28 per cent a borderline, and 43 per cent a normal IVGT.

VI A number of clinical characteristics before and during the acute episode of the myocardial infarction were related to the IVGT determined at the time of discharge from hospital, i.e. usually after 3—4 weeks hospitalization. Patients with diabetic IVGT were significantly taller and heavier than those with normal IVGT and pre-existing arterial symptoms, posterior location of the myocardial infarction, enlarged relative heart volumes and supraventricular ectopic beats (SVEB), atrial fibrillation and/or digitalis treatment were also related to diabetic IVGT. There was no relationship between IVGT and physical working capacity during the follow-up.

VII At discharge from hospital the patients were given *tolbutamide* or a *placebo* according to odd or even birth dates since a double-blind trial was considered to entail too much risk. The 2 groups corresponded in all essential respects. There were 95 patients in the tolbutamide treatment group and 83 controls, mean ages being 59 years. The mean follow-up time was 3 years per patient, range 12 to 66 months. Three participants withdrew from the study after 3, 14 and 22 months.

VIII Long-term tolbutamide treatment did not reduce the total mortality, this being 13 out of 95 compared with 16 out of 83 controls, but over the first 18 months the mortality was significantly lower in the tolbutamide group, i.e. 7 deaths compared with 15 in the control group. The mean survival time of those who subsequently died was also significantly prolonged from 6 months in the controls to 18 months in the tolbutamide-treated patients. All deaths were considered to have been

cardiac. The mode of death was unrelated both to treatment and IVGT The mean k value of those who died was lower than that of the surviving ones (0 96 and 1 17 respectively) As 24 out of a total of 29 who died belonged to the 101 patients with initially abnormal IVGT the decrease in mortality occurred mainly in this category of survivors, which thus constituted a risk group benefiting from prolonged tolbutamide therapy The non fatal recurrences of myocardial infarction were similarily postponed, while no influence upon other cardiovascular manifestations was observed. No serious side effets were seen, and in 76 per cent of the tolbutamide-treated patients the routine dosage of one gram daily in divided doses could be maintained.

IX. Certain clinical characteristics occurring during the hospitalization were found to imply an adverse prognosis in the control group i.e *a*) cardiac complications *b*) "major arrhythmias *c*) ventricular ectopic beats (VEB) *d*) SVEB or atrial fibrillation,) SVEB, atrial fibrillation and/or d gitalis treatment. In patients with abnormal IVGT only the 3 latter characteristics (c *d* &) exerted an adverse influence upon prognosis. Particularly important were *SVEB atrial f brillation and/o d gital s t eatment (e)* as the overall mortality was reduced to 5 per cent in their absence, and they occurred in 27 out of the total of 29 patients who subsequently died.

X Tolbutamide treatment reduced the overall mortality significantly in the patients with VEB However the incidence of this arrhythmia in the present study was approximately half of that now known to occur when continuous ECG monitoring is used Therefore the significance of this finding is difficult to assess. In patients with SVEB atrial fibrillation and/or digitalis treatment indicating heart failur the beneficial influence of tolbutamide treatment upon survival was similar to that seen for the total series

XI. The IVGT was followed by annual retests. *In the cont ols no significant alteration occurred* in those with initially normal IVGT while a significant *impairm nt* was apparent after 3 years in those with *diabetic IVGT* and after 4—5 years in those with *abnormal IVGT* Three out of 18 surviving controls with *initially* diabetic IVGT developed overt diabetes mellitus during the follow-up none in the other 2 IVGT groups.

XII A significant *improvement* in IVGT in the *tolbutamide-t eated patients* was seen in those with *abnormal IVGT* when tolbutamide was withheld for 60 hours prior to the retest, and thus improvement was *still significant after 4—5 years of un*-interrupted treatment. In those with normal IVGT no essential alterations were observed. None of the tolbutamide treated patients developed overt diabetes.

XIII Serum cholesterol and triglyceride were *followed for one year after discharge from hospital* in 18 controls and 28 tolbutamide-treated patients. Serum triglycerides decreased in those of the latter group with abnormal IVGT no other changes were significant.

XIV *Concluding* long-term tolbutamide treatment *was associated with improved survival over* 18 months in survivors from a first myocardial infarction without overt diabetes mellitus, particularly in those with abnormal IVGT in whom it also improved glucose tolerance for 4 to 5 years and decreased serum *triglycerides for at least* one year after the acute episode

A high risk group comprising those with signs suggestive of heart failure appeared to benefit particularly from the treatment.

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The Electrophoretic Mobility of Red Cells and Platelets and the Plasma Viscosity in Coronary Heart Disease

By Kari Karppinen

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THE ELECTROPHORETIC MOBILITY OF RED CELLS AND PLATELETS AND THE PLASMA VISCOSITY IN CORONARY HEART DISEASE

BY

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HELSINKI 1970

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Helsinki January 1970

Kari Karppinen

CONTENTS

INTRODUCTION AND PURPOSE OF THE PRESENT STUDY

Increasing attention has been paid in the past few years to the possible significance of changes in the surface electrical charge of red cells, platelets and vascular walls in the pathogenesis of coronary heart disease. The surface charge of a cell sets up an electrostatic force which tends to repel charges of the like sign. According to the theories of colloid stability (Derjaguin and Landau 1941 Verwey and Overbeek 1948) the normal suspension stability of the blood is closely dependent on the electrical repulsion between the cells. Some electrical characteristics of cell surface can be studied by means of cell electrophoresis.

The results reported in the literature on the significance of the electrical factors on the cell surface in coronary heart disease are conflicting and some of the studies are open to criticism in methodical respects. For example, sufficient attention has not always been given to the significance of plasma factors, especially of plasma viscosity in th interpretation of the results of cell electrophoretic studies.

The present investigation was undertaken with the object to study by means of cell electrophoresis the surface charge of red cells and platelets in patients with coronary heart disease as compared with healthy persons and to examine the viscosity of the plasma and its effect on the electrophoretic mobility of cells in these two groups.

Some of the present data have been published as a preliminary report (Karppinen 1968)

trode (e.g. silver/silver chloride, copper/copper sulfate or zinc/zinc sulfate electrodes) and the irreversible platinum electrode.

Cell electrophoresis in biochemical studies

The structure of the outer portion of the cell membrane has been investigated by means of a combination of chemical and enzymatic treatment of the cells, coupled with electrophoretic measurements, the latter being a convenient means of detecting changes in the ionic composition and the structure of the cell surface. The neuraminidase of the influenza virus and Vibrio cholerae has been found to reduce markedly the electrophoretic mobility of red cells (Hanig 1948 Ada and Stone 1950) Piper (1957) was the first to demonstrate definitely by means of cell electrophoresis that the surface charge of red cells is mainly due to neuraminic acid which is one of the sialic acids. Later investigators (Cook et al 1961 Ruhenstroth-Bauer et al 1962, Eylar et al. 1962 Seaman and Uhlenbruck 1963) have corroborated this observation and have shown that the charged carboxyl groups of sialic acid are the determining factors in the electrical charge. It has been demonstrated that treatment with neuraminidase can reduce cell mobility by as much as 94 per cent (Eylar et al 1962) The importance of neuraminic acid in the surface charge of leucocytes (Ruhenstroth-Bauer et al. 1962 Rueff 1964) and thrombocytes (Jerushalmy et al. 1961 Madoff et al 1964) has also been verified.

The precise function of sialic acids is not known Removal of sialic acids is associated with changes in the antigenic character and survival of erythrocytes (Brading et al 1959 Springer 1963) the leucocyte metabolism (Fisher and Ginsberg 1956) and the adhesiveness of malignant cells to vascular endothelium (Gasic and Gasic 1962) Alteration in the deformability of cells may also depend on their surface charge characteristics (Weiss 1965) It has been suggested (Gottschalk 1960) that the presence of the charged carboxyl groups of the N acylated neuraminic acids confers "structural rigidity on the underlying protein core

Correlation has been found between the charge density of sea-urchin eggs and their adhesion to glass (Dan 1947) It has been demonstrated (Nordling 1967) that anionic polymers, which reduced the adhesivity of HeLa cells, increased the surface charge of these cells. A close correlation existed between the change in charge density and the reduction of adhesion A correlation has also been found between the charge density and erythrocyte aggregation (Pollack et al 1965) and the flocculation of leucocytes (Wilkins et al 1962 a, b)

Electrophoretic studies of tumour cells

Ambrose et al. (1956) were the first to report a difference in the electrokinetic charge between normal kidney cells and homologous tumour cells of the hamster Purdom et al. (1958) observed a correlation between the progression or increase in malignancy of the mouse sarcoma and the corresponding increase in surface charge density of its individual cells. On the other hand it has been found (Heard et al 1961 Ruhenstroth-Bauer and Fuhrmann 1961 Eisenberg et al. 1962) that certain types of cells derived from embryonic or regenerating tissue have a higher negative surface charge than cells from the corresponding adult homologous tissue so that an increased electrophoretic mobility may also be associated with the normal growth process The surface charge of human carcinoma cells has been observed to be greater than that of the corresponding normal cells (Ruhenstroth Bauer et al. 1962 Rueff 1964) whereas it also has been reported (Vassar 1963 a, b Simon-Reuss et al. 1964) that epithelial malignant tumour cells do not reveal a particularly higher electrophoretic mobility On the other hand the human mesenchymal tumour cells have a higher charge than human carcinoma cells, and neuraminidase produces a more pronounced decrease in the charge of the mesenchymal tumour cells (Vassar 1963 b)

Cell electrophoresis in bacteriology and virology

Cell electropho esis combined with enzymatic and chemical treatment of the cells had added to our knowledge of the surface characteristics and structure of bacteria as well as of factors that may have an effect on the cell surface for example certain drugs and desinfectants (Bazin and Alliot-Conade 1946 Dyar and Ordal 1946 McQuillen 1950 a b 1951 a b Barry and James 1952, Chaplin 1952 Lerche 1953 1954 1955 Santorato 1953 Haydon 1956 James 1965) In virological research, cell electrophoresis has made it possible to explain certain viral effects on the cell surface e.g haemagglutination caused by vira (Hanig 1948 Ada and Stone 1950 Sachtleben 1959 Straub 1961 1963)

Application of cell electrophoresis in clinical studies

Red cell and platelet electrophoretic mobility in atherosclerotic vascular disease

Electrophoretic mobility of red cells The electrophoretic mobility of red cells in plasma has been found to be slower on the average in patients with coronary heart disease than in healthy persons (Davies 1958 1959 Davies and Clark 1961) It has even been claimed that "the erythrocyte migration time appears to provide a more satisfactory index of atheroma than the serum cholesterol level for the study of individual patients (Davies 1959) When measured in phosphate buffer on the other hand the red cell mobility did not differ from that of the controls (Davies 1958) On the base of these observations the theory was presented (Davies 1965) that patients with coronary disease and other conditions related to atherosclerosis have n the plasma surface active substances" that by adsorption to the surface of particles may change their surface charge. Changes in plasma surface activity were said to be related to increased platelet aggregation and adhesiveness (Davies 1967)

In studying 50 patients with occlusive arterial disease, 16 of whom had angina pectoris and 20 myocardial infarction, and 50 control subjects Begg et al (1966) found that the red cell mobility both in plasma and in phosphate buffer was slower in the patient group than in the control group They concluded that patients with occlusive arterial disease therefore have one or more factors in the plasma and also in their red cells which reduce the surface charge of the cells and they thought that these "slowing factors by facilitating red cell aggregation may play a part in the pathogenesis of occlusive arterial disease. No difference from the normal was seen in the mobility of red and white cells by Ruhenstroth Bauer et al. (1961) in 3 patients with myocardial infarction Rottino and Angers (1961) reported that the mean red cell mobility in serum was in 200 normal subjects 1.27 (S D 0 05) μ/sec/V/cm and in 10 patients with myocardial infarction slightly slower with a mean value of 1 16 μ/sec/V/cm.

Electrophoretic mobility of platelets The electrophoretic mobility of thrombocytes in the plasma was observed by Hampton to be greater in patients with coronary heart disease than in control subjects (Bolton et al 1968) Gröttum (1968) on the other hand observed no significant difference in thrombocyte mobility in plasma in 1 patients with cardiovascular disease as compared with 50 healthy controls. In normal persons there is a biphasic response of platelets to the aggregating agents ADP and noradrenaline concentrations of ADP and noradrenaline of the order that cause platelet aggregation bring about a decrease in mobility and lower concentrations cause an increase in mobility (Hampton and Mitchell 1966 a) In patients with ischaemic heart disease and peripheral vascular disease there has been found a selective increase in sensitivity to ADP (Hampton and Mitchell 1966 b Hampton et al. 1967) The abnormal platelet behaviour was suggested to be determined by abnormalities in the plasma system which included two components one

was stable and was associated with the lecithin of the low-density lipoproteins, and the other was labile and appeared to be an enzyme. Gröttum (1968) observed that ADP and nor adrenaline decreased the mobility of thrombocytes, but no biphasic response was seen

Cell lectrophore s in other clinical conditions

Differences from the normal in the surface potential of leucocytes in the peripheral blood have been observed in patients with leucaemia, bone marrow metastases from malignant tumours, lymphosarcoma, or osteosarcoma and in patients with advanced ostitis fibrosa, osteoclastoma, acute osteomyelitis, L.E.D or tonsillar sarcoma, rather typ cal Hämozytopherogramme" having been described for these diseases (Ruben stroth-Bauer et al. 1961 Rueff 1964) For the present however this method of examination has not attained diagnostic importance.

Whole blood and plasma viscosity in coronary heart disease

D terminants of whole blood and plasma viscosity

Blood is rheologically a non-Newtonian fluid, i e. it does not obey the law f Poiseuille (Merrill and Wells 1961 Dintenfass 1964) and its pparent viscosity is dependent on shear rat and shear stress. Factors that influence blood and plasma viscosity have been studied among others, by Dintenfass (1964 a) Merrill et al. (1964 a, b) This topic has been recently reviewed by Somer (1966) Factors influencing the viscosity of whole blood are mainly the haematocrit value the degree of aggregation of the red cells, the viscosity of the plasma and a sol-gel transformation in the interior of red cells. The viscosity of blood increases markedly as the rate of shear decreases. It has been suggested that a critical factor in the development of these changes is reversible cell aggregation, principally in the form of "rouleaux" (Dintenfass 1962 Merrill et al 1963) The reversibility is credited to the breaking down of rodlike rouleaux structures under increasing shear with re-formation as the rate of shear returns to zero The principal plasma factor for cell aggregation in normal subjects has been shown to be plasma fibrinogen. Blood viscosity may also be influenced by the size and shape of the red cells which in turn are affected by the pH level and osmolality On the other hand the part played by leucocytes and thrombocytes in blood viscosity in healthy persons has been found to be negligible. Likewise changes in the blood lipids have also not been found to be reflected as constant changes in blood viscosity

A correlation has been found to exist between plasma viscosity and the protein concentration and the size and shape of the protein molecule also have a definite influence (for review see e.g Somer 1966) Thus spherocolloids show a rather weak dependence between the viscosity and the concentration whereas fibrous proteins may produce a high viscosity even in dilute solutions (Eastham and Morgan 1965) There are very few studies of the effect of various lipids, and their significance in this respect is so far not clear Dintenfass (1965) stated that t 20 C the viscosity of lipid-containing plasma was fivefold that without lipids, but at 37 C the effect was not noted Gelin et al. (1968) reported in a preliminary study that 4 patients with hypercholesterolaemia had a slightly higher viscosity of both plasma and whole blood than normal subjects. The relationship between serum viscosity and lipids was studied by Shinagawa (1964) who found a statistically significant positive correlation between the serum viscosity and the serum levels of beta-l poproteins total cholesterol phospholipids and triglycerides.

Vi osity measu ments in o ona y heart diseas

There are relatively few studies concerning blood and plasma viscosity in coronary heart disease and the findings are contradictory Kellogg and Goodman (1960) using a capillary type viscometer observed an increased viscosity

of whole blood and plasma in the acute phase of myocardial infarction The increase in the viscosity was correlated to the increase in the plasma fibrinogen concentration Other workers have found the latter concentration to be higher in patients with coronary heart disease than in healthy controls (McDonald and Edgill 1957 Merskey et al 1960 Pilgeram 1961 Katz et al 1963 Hampton et al 1966) though this observation has not been confirmed by all (Naimi et al 1963 Pedersen and Persson 1967) Mayer (1964) also using a capillary viscometer found above normal blood and plasma viscosities in chronic coronary disease, and Shinagawa (1964) observed that viscosities of sera in coronary patients were about 5 per cent higher than those of normal sera.

Increased blood viscosity after myocardial infarction has been observed with the rotation viscometer method (Dintenfass 1964 a, b Dintenfass et al 1966 Kallio et al 1967 Pedersen and Persson 1967 Ditzel et al 1968) but the findings of increased blood viscosity in coronary heart disease have not been corroborated by all (Rosenblatt et al. 1965 Begg and Hearns 1966 Rozenberg 1968) As was stated above, the haematocrit value is an important determinant of blood viscosity The mean haematocrit values in coronary patients have been found to be elevated over the values in healthy subjects (Burch and De Pasquale 1961 1962, Mayer 1965 Stables et al. 1967) though most investigators have not confirmed this observation (Conley et al. 1964 Vuopio and Eisalo 1964 Rosenblatt et al 1965 Hatch et al 1966 Dintenfass et al. 1966 Rozenberg 1968)

Patients with coronary heart disease

Fifty five patients with coronary heart disease (CHD) were studied Forty-eight of them had had previous clinically verified myocardial infarction and 7 patients had clinically typical angina pectoris without known myocardial infarction. The series was divided into three age groups as is seen in Table 1 The mean age of this series was 51 4 years. The series included businessmen and office and factory workers. Coronary heart disease did not imply complete physical inactivity in any of the cases.

Table 1 Age distribution and number of subjects in the control and the CHD series.

		< 45 years	45–54 years	≥ 55 years
Control subjects	N	19	18	11
	Mean age	39.3	50 4	59 1
Coronary patients	N	14	22	19
	Mean age	41 4	49.5	60 9

In the patients who had had myocardial infarction the present investigation was carried out not earlier than 10 weeks after the occurrence of infarction to eliminate the possible influence of its acute effects. The time lapse from the infarction ranged from 10 weeks to 10 years; in most cases it was 2 to 3 years The criteria for myocardial infarction were the clinical picture electrocardiographic changes and/or typical laboratory test results (erythrocyte sedimentation rate leucocyte count, and serum enzyme determinations) Clinical data were available for all the infarction patients

The electrocardiograms taken at the time of the present study showed in the case of 19 patients with infarction (40 per cent of the series) the typical QRS changes due to a myocardial lesion, by means of which it was possible to localize the site of infarction. Three patients with a myocardial infarct also exhibited the QRS changes but an exact localization of the lesion was not possible. Five patients (10 per cent) had depressed ST segments and ischaemic negative T waves and 7 patients (15 per cent) unspecific slight ST changes or intraventricular conduction disturbances No definite deviation from the normal was seen in the electrocardiograms of 14 patients with infarction (29 per cent)

In the 7 cases without known myocardial infarction the diagnosis of coronary heart disease was based on the typical history of angina pectoris In the resting ECG one of these patients had ischaemic T wave changes, 2 patients an unspecific depression of the ST segment or an intraventricular conduction disturbance, and 4 patients a fully normal ECG pattern

The symptoms of the CHD patients at the time of this study included severe or moderately severe angina pectoris of effort in 20 patients and angina of mild degree in 24 patients; 11 patients had no cardiac symptoms. Mild cardiac insufficiency was experienced by 5 patients and claudication by 4 None of the patients had manifest congestive heart failure at the time of the study Eight patients were using digitalis and one received mild diuretic therapy Other significant diseases were not diagnosed in any of the patients. No one was on anticoagulant therapy or received long acting coronary dilatating" drugs

Control subjects

The control series consisted of 48 apparently healthy men ranging in age from 34 to 66 years The controls were selected so as to obtain about the same age grouping as in the patient series (Table 1) The mean age was 48 0 years.

To obtain some information on obesity in the examined groups a weight/height index was calculated as

$$\frac{\text{weight (kg)}}{\text{(height 100) cm}}$$

The mean weight/height index was 1 04 (S.D 0 12) in the CHD series and 1 06 (S D 0 11) in the control series. An index value of 1 10 or over was encountered in 26 per cent of subjects in the former series and in 31 per cent of subjects in the latter

The subjects were examined either as outpatients or during examination period of 2–3 days in the hospital. A detailed history concerning previous diseases and present state of health was obtained and a physical examination was performed. The blood pressure was measured in the supine position blood pressure below 160/100 being regarded as normal. Conventional 12 lead electrocardiograms were taken and radiological examination of the heart and lungs was performed.

The blood samples were drawn between 8 00 and 9 00 A.M. after overnight fasting and before the morning meal. Minimal stasis was used before taking the blood sample from the antecubital vein. The sample was taken into three centrifuge tubes, one of which was heparinized (about 100 units/ml blood) in order to yield plasma sample, one was unheparinized and was used for the separation of serum, the third tube was needed for the measurement of plasma fibrinogen. At the same time a 150 ml sampl was taken (1 volume of 3 4 per cent sodium citrate and 9 volumes of blood) for the measurements of red cell and platelet electrophoresis, plasma specific conductance and plasma relative viscosity Capillary blood samples for routine haematological studies were taken and treated by the usual laboratory techniques.

The oral glucose tolerance test was performed after overnight fasting on the following morning; the subjects had eaten a carbohydrate rich meal on the preceding day The test load of glucose in 10 per cent solution was 1 gr/kg body weight. Blood samples were drawn before the test and 1/2, 1 1 1/2 2 2 1/2 and 3 1/2 hours after the glucose intake. During the test the subjects were in bed or on a chair and smoking was not allowed

Cell electrophoresis

Red cell electrophoresis

Red cells were washed three times in 0 145 M NaCl and suspended as a 0 02 per cent solution in plasma or M/15 phosphate buffer (pH 7 3)

Nine volumes of blood were collected from an antecubital vein into a siliconized bottle containing one volume of trisodium citrate (3 4 per cent w/v) The sample was first centrifuged at 250 g for 10 minutes at room temperature to get platelet-rich plasma (PRP) Platelet poor plasma (PPP) was prepared by centrifugation at 700 g for 15 minutes. Thereafter the sample was centrifuged at 1500 g for 15 minutes to yield plasma for the red cell suspension All measurements were made within 4 hours after collecting the blood

The electrophoretic mobility of cells was measured in a cylindrical tube apparatus described by Bangham et al. (1958) The horizontal tube was immersed in a water bath at 25 $\pm$ 0 1 C. The times for the cells to traverse 20 μ in alternate directions were recorded with a stopwatch to an accuracy of $\pm$ 0 05 sec. The field strength was kept constant at 3 13 V/cm which was calculated by dividing the voltage between the electrodes (50 V) by the effective distance between the electrodes. The effective electrical length (l_e) was calculated from the current (I) cross-sectional area of the tube and the known specific conductivity of the electrolytic solution (K) and is given by·

$$l_e = \frac{KV\pi a^2}{I}$$

where V is the applied potential and a is the radius of the capillary The electrical length was found to correspond closely to the physical length of the tube.

A minimum of 8 cells were timed in most cases 10–15 cells, and the average mobility was

calculated. The electrophoretic mobility was expressed as μ per second per 1 per cm (μ/sec/1/cm)

Platelet electrophoresis

The electrophoretic mobility of platelets was measured in a plasma sample containing one volume of PRP and 9 volumes of PPP. The procedure of measurement was otherwise the same as with red cells. The measurements were begun one hour after centrifugation to allow for the decrease in electrophoretic mobility of platelets which takes place during the first hour (Hampton and Mitchell 1966 c)

The electrophoretic mobility of red cells and platelets in plasma were corrected to the viscosity of distilled water at 25 C. No correction was made for the dielectric constant of the plasma.

Determination of the stationary level

All measurements of cell electrophoresis were made in the stationary layer i.e. the level in the tube where there is no endosmotic movement of the suspension medium. The level was determined by calculating it by the Lamb equation (1888) and experimentally with human red cells (Bangham et al 1958). The electrophoretic mobility of washed human erythrocytes in 0 145 M sodium chloride solution with added 0 145 M hydrochloric acid or sodium hydroxide solution is constant over the range of pH 5 to 9. Haemoglobin in dilute solution which does not adsorb onto the red cells has no effect on the cell mobility but because of its adsorption to the glass wall and its different charge densities at different pH values it can alter the endosmotic movement of the suspension medium. It is thus possible to locate the position of the stationary level experimentally as the point of intersection of a series of depth-velocity curves at various values of pH. Both of the methods gave identical results. The normal mobility of red cells in 0 145 M sodium chloride solution at the stationary level was found to be 1 08 S D 0.03 μ/sec/V/cm, and it was therefore possible to test the location of the stationary level with normal red cells before the measurement of cell mobility

Preparation of electrodes. One of the major sources of error in determination is the polarization which arises at the boundary between the electrodes and the sample to be examined. Platinum electrodes were chosen for the present study because of their low polarization simpler construction as compared with reversible silver/silver chloride or copper/copper sulphate electrode systems, and because there is no risk of contamination by toxic ions contrary to the reversible electrodes. The platinum electrodes permit the application of a fine porous coat of platinum black which markedly reduces the polarization. The procedure in applying the platinum black to the platinum electrodes was that recommended by Schwan (1963). Because platinum black covered electrodes always deteriorate with use, the procedure should be renewed from time to time.

Cleaning of the electrophoretic apparatus. The chamber was cleaned occasionally with CrO_3/H_2SO_4. With cleaning mixtures containing chromium it was necessary to have distilled water in the chamber overnight so as to ensure that the capillary wall was effectively free of adsorbed chromium ions. Between measurements the cell was flushed out with distilled water followed by the appropriate suspending fluid. After a system containing proteins had been examined the chamber was rinsed out first with aqueous M sodium chloride solution, followed by distilled water and thereafter by suspending medium.

Plasma relative viscosity

The plasma relative viscosity was measured from heparinized and citrated plasma with the Harkness (1963) viscometer (Coulter Electronics Ltd., England). The viscometer was mounted in a waterbath and the temperature was maintained at 25 ± 0 1 C by means of an accurate thermostat. The length of the capillary was

200 mm and the diameter 0.3 mm. The time of flow was displayed on an electrical timer accurate to 0.01 second. For each measurement 2 ccm of plasma was needed. Three estimations were performed and the average value was calculated. The instrument was calibrated against distilled water.

Electric conductivity of the plasma

The conductivity of the plasma sample was measured with a specially constructed apparatus consisting of a measuring bridge in combination with a conductivity cell. The bridge comprised a Wheatstone bridge fed by A.C. at 1000 c/s from a low frequency oscillator. One branch of the measuring bridge was a 10-turn adjustable potentiometer, two others were matched fixed resistors, and the final branch was the resistance to be measured. The conductivity cell was chosen from the Philips series type PR 9512/01 (with cell constant 1.42) suitable for measurements on small volumes. After being amplified, the unbalanced voltage of the bridge was passed to a zero indicator, a galvanometer in this apparatus. All the measurements were made at 25 ± 0.1 C.

Haematological and biochemical methods

The *haemoglobin concentration in blood* was measured colorimetrically as cyanmethaemoglobin. The standards were obtained from the Central Laboratory of the Finnish Red Cross Blood Transfusion Service, Helsinki.

The *erythrocyte sedimentation rate* of one hour was determined by the method of Westergren.

The *haematocrit values* (vol. per cent) were determined in duplicate from capillary samples with the Hawksley micro-haematocrit centrifuge.

Blood sugar was determined from samples of capillary blood by a modified method in which deproteinization of the blood was carried out with zinc sulphate and sodium hydroxide according to the method of Somogyi (1945) and the sugar was determined by the standard colorimetric method described by Hammarsten (1935).

Serum cholesterol was determined in duplicate samples by the Anderson and Keys (1956) procedure of the method of Abell et al. (1952). The samples were stored in a freezer at –20°C. Standard samples were always run simultaneously.

Serum triglycerides were determined by the method of Carlson and Wadström (1959) but the extraction and purification of triglycerides was performed according to van Handel and Zilversmit (1957) with a mixture of chloroform and zeolite (Doucil, W.A. Taylor Company, U.S.).

Fibrinogen content of the plasma was determined in duplicate according to the method of Ratnoff and Menzie (1951). All the measurements were performed at the Central Laboratory of the Finnish Red Cross Blood Transfusion Service, Helsinki.

Serum uric acid was determined in duplicate by the uricase method (Praetorius and Poulsen 1953, Bergmeyer 1962, Hyvärinen et al. 1965 b). Uricase "Leo" (Leo Pharmaceutical Products, Denmark) was used as the enzyme preparation.

Statistical procedures

Conventional statistical methods and measures were used. The statistical significances of the differences between the examined groups were determined by Student's t-test or chi-square test, and the correlations were studied by means of linear regression analysis. The tables of Geigy (1960) were used.

RESULTS

Haematological and biochemical data

The haematological and biochemical data presented below were determined in this material in order that the changes possibly encountered in plasma viscosity and cell electrophoretic mobility could be correlated to these values. A more detailed characterization of the material was also possible with the aid of these data.

Haematological data

The haematological data are given in Table 2 as mean values with corresponding standard deviations and ranges. The haematocrit level was 46.5 (S D 3 0) per cent in the CHD series and 46 9 (S.D 3 8) per cent in the control series, and there accordingly was no statistically significant difference between the series. Neither were any significant differences seen in the other haematological data

Serum cholesterol

The serum cholesterol content was determined in all the CHD and control subjects. The data are given in Table 3 as mean values with *standard deviations, grouped according to the* age of the subjects.

In the CHD series the serum cholesterol ranged from 186 to 380 mg/100 ml and in the controls from 163 to 324 mg/100 ml. The mean cholesterol concentration in the former group was 269 6 mg/100 ml which was significantly ($p < 0\ 005$) higher than the mean value in control subjects, 238 4 mg/100 ml. In the three age groups the mean serum cholesterol level was somewhat higher in each group of the CHD series than of the control series. The age groups, however were too small to permit the drawing of any definite conclusions.

Table 2 Haematological data in the control and the CHD series.

		Control subjects N 48	Coronary heart disease N 55
Hemoglobin, g/100 ml	Mean ± S.D.	14.7 ± 1 1	14.5 ± 1 1
	Range	11.2 – 17.0	12.7 – 17.5
Haematocrit, %	Mean ± S.D	46.9 ± 3.8	46.5 ± 3.0
	Range	35–55	40–53
Red cell count, millions/cu.mm	Mean ± S.D	4 91 ± 0.36	4.86 ± 0.37
	Range	3.75 – 5.50	4 17 – 5.94
Mean corpuscular hemoglobin, μμg	Mean ± S.D	30.0 ± 1.2	29.8 ± 1.0
	Range	25.5 – 32.7	28 – 32
White cell count, thousands/cu.mm	Mean ± S.D	6.400 ± 1.910	7 100 ± 2.140
	Range	3.600 – 11 400	4.000 ± 14 700
Erythrocyte sedimentation rate mm/h	Mean ± S.D	6.3 ± 4.4	10.9 ± 10.5
	Range	1 – 20	1 – 49

Serum triglycerides

The serum triglyceride content was determined in 53 CHD patients and 48 control subjects. The data are given in Table 3 as mean values with standard deviations, grouped according to the age of the subjects.

In the CHD series the triglyceride levels ranged from 50 to 286 mg/100 ml and in the controls from 42 to 277 mg/100 ml. Comparison of CHD subjects and healthy controls revealed a slightly higher mean triglyceride content in CHD subjects, the mean values being respectively 121.7 and 113.8 mg/100 ml, but the difference was not statistically significant.

When the present series were divided into two age groups, i.e. subjects under 50 years and those 50 years o over, the mean triglyceride level in the younger group of control subjects was 94.0 mg/100 ml. This was a significantly lower value ($p < 0.005$) than in the older subjects with the mean value of 135.4 mg/100 ml. In the coronary patients the younger group also showed a lower mean value of serum triglycerides than the older patients (values 114.2 and 126.5 mg/100 ml, respectively) but the difference was not statistically significant.

Serum ur c acid

The data from the serum uric acid determinations are shown in Table 3. The range of serum uric acid values was from 1.2 to 8.2 mg/100 ml in the CHD series and from 3.9 to 8.4 mg/100 ml in the controls, and the respective mean values were 5.40 and 5.57 mg/100 ml. The difference between the two series was not statistically significant. Concentrations of 7 mg/100 ml and over were encountered in the CHD series in 11.1 per cent of cases and in the control series in 8.3 per cent. Any dependence of the serum uric acid concentration on the age of subjects could not be found.

Plasma fibrinogen

In Table 4 are presented the data from the plasma fibrinogen determinations. In the CHD patients the range of values was from 165 to 450 mg/100 ml and in the controls from 145 to 385 mg/100 ml. The coronary patients showed a significantly higher ($p < 0.05$) mean plasma fibrinogen content, 294.3 mg/100 ml, than the healthy controls, 267.0 mg/100 ml. The mean level in the older subjects was in both series higher than in the younger group but the difference was not statistically significant.

Oral glucose tole ance test

The data from the glucose tolerance test are given in Table 5. The fasting blood glucose was 82.3 (S.D. 13.4) mg/100 ml in CHD series and 86.5 (S.D. 11.1) mg/100 ml in control series. The glucose levels 1/2 hour after the test load

Table 3 Serum cholesterol, triglyceride and uric acid levels in the patients with CHD and in the healthy controls, grouped according to age

	Coronary heart disease				Control subjects			
	<45 years	45–54 years	≥55 years	Total	<45 years	45–54 years	≥55 years	Total
N	14	22	19	55	19	18	11	48
Cholesterol, mg/100 ml								
Mean	279.0	260.6	273.2	269.6	24[illegible].8	226.3	250.6	238.4
± S.D.	± 55.6	± 46.3	± 53.5	± 50.9	± 46.5	± 52.8	± 35.4	± 46.9
Triglycerides, mg/100 ml								
Mean	115.8	113.0	135.8	121.7	96.4	123.5	128.1	113.8
± S.D.	± 32.1	± 43.3	± 62.4	± 49.1	± 25.7	± 60.5	± 46.9	± 47.4
Uric acid, mg/100 ml								
Mean	5.68	5.34	5.25	5.40	5.55	6.06	5.17	5.57
± S.D.	± 0.99	± 1.63	± 1.68	± 1.50	± 0.78	± 1.26	± 1.33	± 1.15

Table 4 Plasma fibrinogen level in the CHD patients and healthy persons, grouped ccording to age.

	Coronary heart disease				Control subjects			
	<45 years	45–54 years	≥55 years	Total	<45 years	45–54 years	≥55 years	Total
N	14	22	18	54	19	18	11	48
Fibrinogen, mg/100 ml								
Mean	280 6	286.3	314.8	294.3	259.8	273.9	277.3	267.0
± S.D.	± 81.2	± 55 7	± 66.1	± 66.8	± 45.8	± 46.3	± 46.3	± 47 4

Table 5 Blood sugar values during oral glucose tolerance test in 53 patients with CHD and in 48 healthy controls

		Fasting	½ h	Peak BS	1 h	1 ½ h	2 h	2 ½ h	3 ½ h
Coronary heart disease N 54	Mean	82.3	168.4	177.2	154 1	123.8	101.0	76.6	65.1
	± S D	± 13.4	± 28.4	± 32.9	± 41 4	± 42.4	± 38.5	± 30.9	± 16.3
Control subjects N 48	Mean	86.5	162.8	164 4	135 7	109.0	90.3	68.2	62.7
	± S.D	± 11 1	± 24.3	± 24.8	± 31 4	± 22.9	± 21 0	± 16.9	± 8.0

Table 6. Percentage of subjects with hump-type curve, "prolonged-type" curv peak blood sugar alues ≥ 180 mg/100 ml, and 2 hour alues ≥ 120 mg/100 ml during oral glucose tolerance test in the CHD and the control series.

		Hump-type"	Prolonged-type"	Peak BS ≥ 180 mg/100 ml	2 hours ≥ 120 mg/100 ml
Coronary heart disease	N	9	21	23	14
	%	16.7	38.9	42.6	25.9
Control subjects	N	9	5	13	3
	%	18.7	10 4	27 0	6.2
	P	N.S.	< 0.01 ($\chi^2 = 9.40$)	N.S.	< 0.05 ($\chi^2 = 6.28$)

were 168 4 mg/100 ml and 162.8 mg/100 ml. At 1 hour the blood glucose level in CHD patients was significantly higher ($p < 0.02$) than in control subjects the values being 154 1 and 135 7 mg/100 ml The glucose levels at also 1 1/2 hour and the top values were significantly higher in the coronary patients ($p < 0.05$)

In the present study the following glucose tolerance values were arbitrarily chosen as normal values 1) fasting value below 110 mg/100 ml 2) peak BS below 180 mg/100 ml 3) value at 1 1/2 hr below 140 mg/100 ml, and 4) at 2 hr below 120 mg/100 ml Glucose tolerance was considered to be reduced when one or more of these borderline values was exceeded

A reduced glucose tolerance was found in 55 6 per cent of patients with CHD and in 29 2 per cent of controls. The difference between the series was statistically significant (chi square test, $\chi^2 = 5.721$ $p < 0.05$)

Table 6 is an analysis of the different types of glucose tolerance curves in the CHD and control series The frequency percentage in each series was calculated for the following·

a) hump-type curve (criteria used peak BS 180 mg/100 ml or over 1 1/2 hr value below

BS = blood suga

140 mg/100 ml, and 2-hr value below 120 mg/100 ml)

b) prolonged type curve, or delayed clearing phase (1 1/2 hr value 140 mg/100 ml or over and/or 2 hr value 120 mg/100 ml or over)
c) peak BS 180 mg/100 ml or over
d) 2-hr value 120 mg/100 ml or over

The hump-type curve was encountered with approximately the same frequency in the two series (16 7 per cent among CHD patients and 18 7 per cent among controls) On the other hand a delayed clearing phase was significantly more common among patients with CHD than among the healthy controls ($p < 0.01$) the incidence being 38 9 per cent and 10 4 per cent, respectively This curve type was encountered more frequently in CHD patients over 50 years of age than in those under 50 ($p < 0.05$) Coronary disease patients had also peak BS values of 180 mg/100 ml or over and 2 hour values of 120 mg/100 ml or over more frequently than the control subjects, but the difference was statistically significant only with respect to the 2-hour value ($p < 0.05$ $\chi^2 = 6.28$)

Comments on the material and the haematological and biochemical data

The common characteristic of the patients studied in the present investigation was coronary heart disease. Patients with previous myocardial infarction and those with angina pectoris without clinically detectabl infarction were considered as one group in the analysis of the results, because the occurence of myocardial infarction may be considered to represent only an episode in the course of chronic coronary heart disease. It is obvious that the control series consisting of middle aged "healthy" men may include some men with latent coronary arterial disease which could not be detected by the method used.

Serum lipids The serum cholesterol level of the patients with coronary heart disease in this study was on the average higher than that of the control subjects. The cholesterol values and their distribution show good agreement with those described in larger series of CHD patients (Pelkonen 1963 Keys et al 1966)

With respect to the triglyceride values, on the other hand the CHD patients showed no statistically significant difference from the controls. This may be due not only to the material being rather small for an analysis of these values, but also to the circumstance that the control series included slightly more obese individuals than the CHD series. The serum levels of glycerides have been related to obesity by a number of authors (Albrink and Meigs 1964 Saller et al. 1966 Abrams et al. 1969) The increase in the serum triglycerides with aging in the normal controls confirms earlier reports on larger series (Schaefer 1964 Fredrickson et al 1967 a Boyns et al. 1969) In the CHD series on the contrary no significant effect of age was observable corroborating the finding made by Pelkonen (1963)

Glucose tolerance A higher incidence of reduced glucose tolerance was found in the CHD patients than in the controls; this agrees well with earlier reports in the literature (reviewed by Wahlberg 1966) The method of glucose determination used in the present study gives higher values than the generally used glucose oxidase (Froesch and Renold 1956) ferricyanide reducing (Hoffman 1937) and ortho-toluidine methods (Hyvärinen et al. 1965 a) For this reason the incidence of abnormal glucose tolerance is slightly higher than if other methods had been employed. This, however does not prevent making comparisons between the two series studied.

The *haematological data* of the CHD patients and healthy controls revealed no statistically significant differences. The studies in the literature in which patients with myocardial infarction had above-normal haematocrit values were made in acute cases, with the exception of the series studied by Mayer (1965) In the acute phase of myocardial infarction the haematocrit values are influenced by changes in plasma volume and by factors that may be correlated to the increased adrenergic drive (Valori et al. 1967 Sedzivy et al 1968) Neither was any

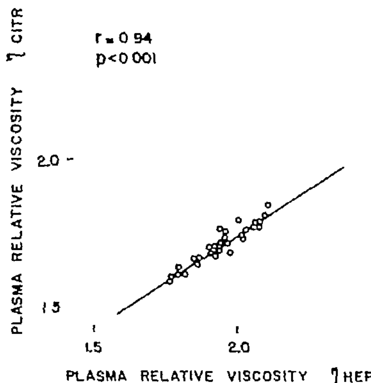


Fig. 1. Relationship between viscosity values of heparinized and citrated plasma in the same individuals. Regression equation $y = 0.653x + 0.440 \pm 0.023$

statistically significant difference found in the mean serum *uric acid* concentration in the two series. The *fibrinogen* content, however, showed a statistically significant difference, corroborating earlier reports in the literature.

Results of plasma viscosity measurements

The plasma relative viscosity was measured from heparinized plasma (heparin c. 100 U/ml blood) and also from 30 samples (14 CHD patients and 16 controls) of citrated plasma (one volume 3.4 per cent sodium citrate in 9 volumes of blood). The plasma samples were prepared by centrifugation at 1 500 g for 15 minutes at room temperature. The values to be compared in the following are the results of viscosity measurements at 25 ± 0.1° C.

Fig. 1 is a comparison of the viscosity values of heparinized (η_{hep}) and citrated (η_{citr}) plasma of the same individuals by the linear regression method. The two values were found to correlate very well, the correlation coefficient being $r = 0.94$ ($p < 0.001$) and the regression equation $y = 0.653x + 0.440 \pm 0.023$. Therefore it was felt justified to calculate, when needed, η_{citr} from η_{hep} by the foregoing regression equation, and thus to avoid measurement of both viscosity values in all the subjects.

The data from the plasma relative viscosity measurements are given in Table 7. The range of the viscosity (η_{hep}) was from 1.73 to 2.23 in the CHD patients and from 1.76 to 2.10 in the healthy controls. The coronary patients had a tendency to a higher mean plasma relative viscosity (1.965) than the controls (1.929), the difference in the present series being significant ($p < 0.05$). The plasma relative viscosity in the younger subjects did not differ statistically significantly from that in the older subjects.

The mean values for η_{citr} were in the coronary patients 1.726 (S.D. 0.069), range from 1.59 to 1.9, and in the controls 1.691 (S.D. 0.064), range from 1.59 to 1.84. The difference between the series with this number of samples (30) was not statistically significant.

Table 7 Plasma relati viscosity values ($\eta_{rel.cap}$ and $\eta_{rel.tr}$) in the CHD and the control series.

		< 45 years	45–54 years	≥ 55 years	Total	$\eta_{rel.tr.}$
Coronary heart disease	Mean ± S.D	1.962 ± 0.084	1.939 ± 0.116	1.975 ± 0 122	1.965 ± 0 122	1 726 ± 0.069
	N	14	22	19	55	14
	Range	1 76 – 2.09	1.81 – 2.23	1 73 – 2 17	1 73 – 2.23	1.59 – 1 79
Control subjects	Mean ± S.D	1.935 ± 0.090	1.918 ± 0 073	1.937 ± 0.088	1.929 ± 0.082	1.691 ± 0.064
	N	19	18	11	48	16
	Range	1 76 – 2.10	1.80 – 2.08	1 79 – 2.09	1.76 – 2.10	1.59 – 1.84

Results of measurements of the electric conductivity of plasma

The electric conductivity was measured from the citrated plasma samples with the conductivity meter The measurements were done in the same thermostate circuit (at 25 ± 0 1 C) as the electrophoretic apparatus. In the coronary patients the conductivity ranged between 0 0117 and 0 0134 mho cm^{-1} with a mean value of 0 0126 (S.D 0 0005) mho cm^{-1} In the healthy controls the mean value was 0 0127 (S.D 0 0003) mho cm^{-1} the range being from 0 0121 to 0 0133 mho cm^{-1}

Results of cell electrophoresis

Red cell electrophoresis

In the following are presented the mobilities of red cells suspended in plasma. The mean red cell mobility in the CHD series was 0.895 (S.D 0.018) μ/sec/V/cm, which was slightly lower than that in the healthy controls, 0 919 (S.D 0 011) μ/sec/V/cm. The difference was statistically significant ($p < 0\ 001$)

It was, however pointed out already by Freundlich (1926) that changes in the electrophoretic mobility of cells may arise from variations in the viscosity of the suspension medium and this has later been demonstrated by many authors (e.g Abramson et al. 1942, Brody 1954 Rueff 1964 Mehrishi and Seaman 1966) For this reason the correlation of cell mobility to plasma viscosity was studied also in the present series. Using linear correlation analysis, the relationship of red cell mobility to plasma viscosity ($\eta_{rel.tr}$) is presented in Fig 2 for the CHD patients and in Fig 3 for the control subjects. In both series a highly significant negative correlation is observed ($p < 0\ 001$) between mobility and viscosity the correlation coefficient ( ) being –0.57 in the former and –0.87 in the latter

Therefore the mobility values observed in plasma were multiplied by a correction factor obtained by dividing the plasma viscosity value by the value of the water at 25 C (i.e. plasma relative viscosity value determined with the capillary viscometer) The product was termed the viscosity-corrected mobility

Table 8 shows the data on the viscosity corrected mobilities of red cells in the CHD and the control series. The mean electro-

Table 8 Viscosity-corrected mobilities of red cells in the CHD and the control series.

		< 45 years	45–54 years	≥ 55 years	Total
Coronary heart disease	Mean ± S.D.	1.538 ± 0.043	1.539 ± 0.055	1.552 ± 0.066	1.543 ± 0.056
	N	14	22	19	55
	Range	1 431 – 1.604	1 458 – 1.648	1 445 – 1.627	1 431 – 1.648
Control subjects	Mean ± S.D	1.559 ± 0 035	1.531 ± 0.037	1.563 ± 0.042	1.557 ± 0.037
	N	19	18	11	48
	Range	1 479 – 1.607	1 466 – 1.627	1 482 – 1.608	1 466 – 1.627
	P	< 0.20	< 0.50	< 0.60	< 0.20

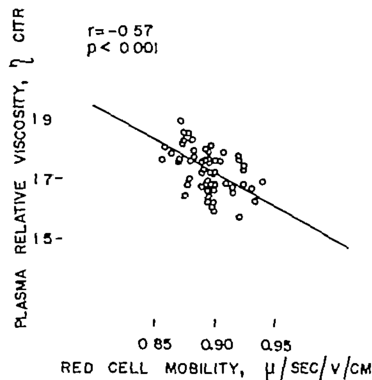


Fig 2. Relationship between red cell mobility (μ/sec/V/cm) and plasma relative viscosity (η_{citr}) in the patients with CHD

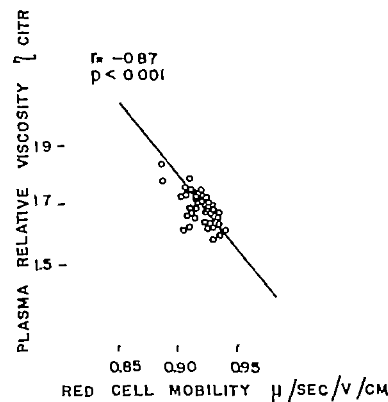


Fig 3. Relationship between red cell mobility (μ/sec/V/cm) and plasma relative viscosity (η_{citr}) in the control subjects

phoretic mobility of red cells in CHD was 1.543 (S.D 0 036) μ/sec/V/cm and in the control subjects 1.557 (S.D 0 037) μ/sec/V/cm. No statistically significant difference was found between the series ($p < 0.20$) Neither was the difference between each pair of age groups statistically significant. A dependence of the mobility values on the age of the subjects could not be detected as can be seen from Table 8

Red cells in buffer Since the various characteristics of the suspension fluid such as viscosity ionic strength, pH and dielectric constant, are known to have a marked influence on the electrophoretic mobility of cells, it was considered advisable to study the surface electric charge of red cells in also a medium in which a variation of the factors mentioned would not be disturbing and the red cells of both series would be in a similar standardized environment. M/15 phosphate buffer (pH 7.3) was chosen as the suspension fluid. The red cell mobility was measured for 13 patients in the CHD series and 11 of the control subjects. The mean value of red cell mobility was 1.287 (S.D 0 015) μ/sec/V/cm in the CHD patients and 1 288 (S.D 0 010) μ/sec/V/cm in the controls. Thus there was no statistically significant difference between the two series with respect to the surface charge of red cells.

Platelet electrophoresis

The mobility of platelets was measured in a sample containing one volume of PRP and 9 volumes of PPP All the measurements were made in the "post contact" state, one hour after the centrifugation of samples (Hampton and Mitchell 1966 c) The mobility of aggregates was not recorded, but it did not differ much from the mobility of single platelets

The mean platelet mobility without the viscosity correction was 0 694 (S.D 0 015) μ/sec/V/cm in CHD and 0 712 (S.D 0 011) μ/sec/V/cm in control subjects. The difference was statistically significant ($p < 0\,001$)

In Fig 4 is shown the correlation between

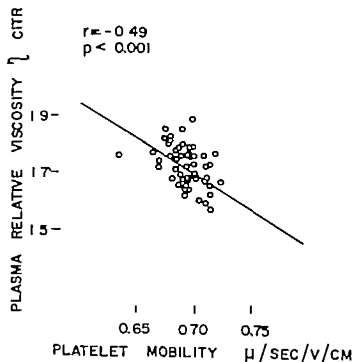


Fig 4 Relationship between platelet mobility (μ/sec/V/cm) and plasma relative viscosity (η_{citr}) in the patients with CHD

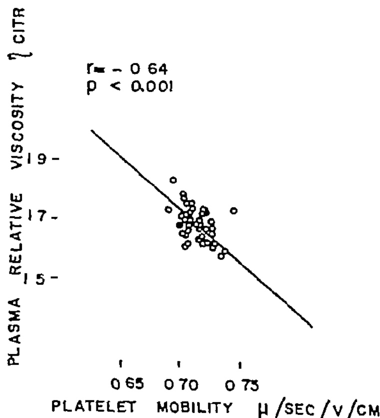


Fig 5 Relationship between platelet mobility (μ/sec/V/cm) and plasma relative viscosity (η_{citr}) in the control subjects.

platelet mobility and plasma relative viscosity (η_{citr}) in the coronary patients as calculated by the linear regression method and in Fig 5 the same in the control subjects. In both series there was a statistically significant negative correlation of the mobility to the plasma viscosity: the correlation coefficient (r) in the former was –0 49 and in the latter –0 64 ($p < 0.001$ in both series)

As in the case of red cell mobility viscosity corrections were made also in the platelet mobility values. In Table 9 are shown the data on the viscosity-corrected mobilities of platelets, expressed as mean values with standard deviations and ranges, grouped according to age of the subjects. In the coronary patients the viscosity-corrected mobility of platelets ranged from 1 118 to 1.319 μ/sec/V/cm, with the mean value of 1 197 (S.D 0 048) μ/sec/V/cm. In the healthy controls the range was from 1 137 to

Table 9 Viscosity-corrected mobilities of platelets in the CHD and the control series.

		< 45 years	45 – 54 years	≥ 55 years	Total
	Mean ± S.D.	1 199 ± 0.044	1.201 ± 0.050	1 19? ± 0.050	1 197 ± 0.048
Coronary heart disease	N	13	21	19	53
	Range	1 132 – 1.253	1 124 – 1.318	1 118 – 1.285	1 118 – 1.319
	Mean ± S.D	1.211 ± 0.030	1 198 ± 0.024	1.215 ± 0.042	1.207 ± 0.031
Control subjects	N	19	18	11	48
	Range	1 164 – 1.249	1 137 – 1.251	1 149 – 1.293	1 137 – 1.293
	P	< 0.50	< 0.90	< 0.20	< 0.20

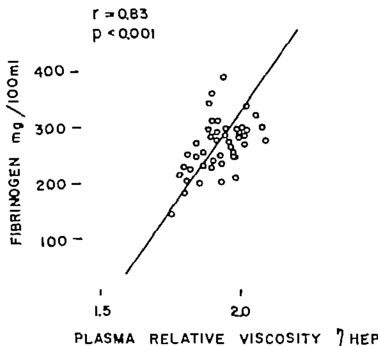


Fig 6 Relationship between plasma fibrinogen concentration (mg/100 ml) and plasma relative viscosity (η_{hep}) in the control subjects.

1.293 μ/sec/V/cm, with the mean value of 1.207 (S.D 0.031) μ/sec/V/cm. The difference between the series was not significant ($p < 0.20$) The same was also true in each of the three age groups separately

Interrelationships of plasma viscosity haematological and biochemical data and cell electrophoresis

Correlation of plasma fib nogen oncentration to plasma v sco ty values

The correlation between the plasma relative viscosity (η_{hep}) and the fibrinogen concentration was studied by linear regression analysis. Fig 6 includes th fibrinogen and η_{hep} values of the control subjects and Fig 7 those of the coronary patients. A highly significant correlation ($p < 0.001$) was found to be present between the plasma relative viscosity and the fibrinogen content in both series. The correlation coefficient (r) in the control subjects was 0.83 which was somewhat better than 0.55 in the coronary series, which may point to differences between th series in the colloids that determine plasma viscosity The regression equation in the control series is $y = 722.7x - 1125.3 \pm 25.9$ and that in the coronary series $y = 395.4x - 483.2 \pm 56.0$

Cor elation of plasma vis osity to reduced glucose tolerance

In the patients with CHD (21) whose glucose tolerance curve was of the prolonged type the plasma viscosity (η_{hep}) averaged 2.003 (S.D 0.037) This was significantly ($p < 0.01$) higher than the viscosity in the other patients with CHD whose plasma viscosity averaged 1.936 (S.D 0.110) When the patients giving a hump-type curve were included in the reduced glucose tolerance group there was no longer a significant difference from the remainder of the CHD series. The number of prolonged-type

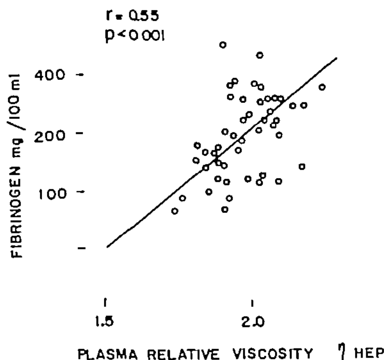


Fig 7 Relationship between plasma fibrinogen concentration (mg/100 ml) and plasma relative viscosity (η_{HEP}) in the CHD patients.

curves in the control series was too small to permit the drawing of any conclusions concerning correlation of reduced tolerance to plasma viscosity

Correlation of plasma viscosity to lipid levels

The plasma viscosity and the cholesterol content of serum showed no correlation in the present series. On the other hand in the highest serum glyceride quartile of the control series the plasma viscosity was significantly ($p < 0.001$) higher than that in the lowest quartile. Coronary patients also had on the average higher viscosity values in the highest serum glyceride quartile but the difference was not statistically significant. The possible reasons for this are the higher fibrinogen content in the CHD series than in the control series and the wider dispersion of the fibrinogen values in the CHD series which may mask the possible influence of other factors on the viscosity

Interrelationships of red cell and platelet mobilities and biochemical findings

The mobilities of red cells and platelets in plasma were studied in the same individual by linear correlation analysis. The results presented in Figs. 8 and 9 show that the mobility values of the two cells have a fairly parallel course Thus the effect of the suspension medium on the surface charge is very similar in red cells and platelets.

On the other hand, a reduced glucose tolerance and the serum cholesterol, triglyceride and uric acid contents were not correlated to red cell or platelet mobility in the present series.

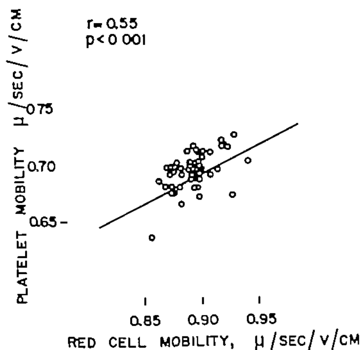


Fig 8. Relationship between red cell mobility and platelet mobility in plasma in th CHD patients.

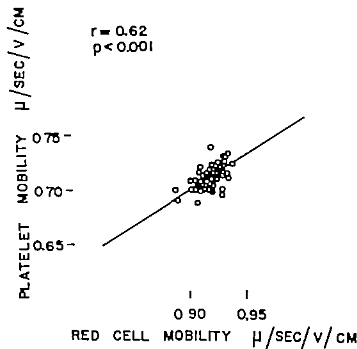


Fig 9. Relationship between red cell mobility and platelet mobility in plasma in the control subjects.

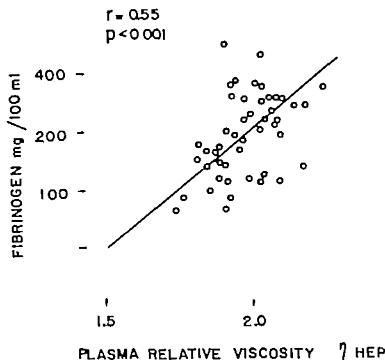


Fig 7 Relationship between plasma fibrinogen concentration (mg/100 ml) and plasma relative viscosity (η_{hep}) in the CHD patients.

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reported by Zucker and Levine (1963) and Gröttum (1968) This variability in the results may be due mainly to suspension fluid properties that influence the mobility of cells and to differences in the methods of measurement of these properties, as discussed in connection with red cell electrophoresis.

Cell electrophoresis in coronary heart disease

Red cells

In examining the results of the present study on the mobility of red cells in plasma it is observed -- as also was done by Davies (1958 1959) Davies and Clark (1961) and Begg et al. (1966) -- that the mobility is slower in patients with CHD than in healthy control subjects. This finding is not, however sufficient for the drawing of conclusions concerning the difference in the cell surface charge in the two series. It is necessary also to take into consideration possible differences in the viscosity of the suspension fluids used which have an influence on cell mobility Viscosity corrections were not made by the investigators cited. As was shown above the plasma viscosity correction eliminated the difference between the series with respect to red cell mobility In their studies Davies and Begg et al. also used remarkably long cell migration times, which also increased the possibilities of error in the mobility values (polarization shift from the stationary level convection currents)

Neither was any correlation found in the present study between cell mobility and serum cholesterol content, and there was accordingly no evidence to support the assumption that non-ionogenic cholesterol would by adsorption to the cell surface, diminish the electrostatic repulsion between cells by substituting for the ionogenic groups on the cell surface (Edit. Brit. Med. J 1962, p 108) The erythrocyte surface has proved to be relatively inert as an adsorbing agent, and according to Heard and Seaman (1960) some 10 per cent of the surface would have to be composed of cholesterol before its electrophoretic behaviour would be detected The "change in plasma surface activity" and the "slowing factors" suggested by Davies and Begg in patients with CHD may be explained at least for the greater part, by a change in plasma viscosity

No difference between the CHD and the control series was observed in red cell mobility when measured in phosphate buffer solution. This accords well with reports in the literature of a stable red cell surface charge. The finding that the red cells of patients with atherosclerosis would move in buffer solution more slowly than those of normal individual (Begg et al. 1966) probably has its only explanation in the methodical reasons referred to above.

Platelets

Also the platelets of the patients with CHD had a lower mobility in plasma than the platelets of the control subjects, but after the plasma viscosity correction there no longer was any difference that would point to a difference in the surface charge. Gröttum (1968) also found no significant difference in the platelet mobility of patients with cardiovascular disease and in healthy control subjects, although numerically the patient series had slightly higher values. His patient series was rather small consisting of 15 patients, 10 of whom had acute myocardial infarction, and it is therefore not fully comparable to the present material in which the patients were examined in a "stable phase" in order to eliminate the changes occurring in the haematocrit and viscosity values during the acute phase. On the other hand Hampton's observation (Bolton et al. 1968) that persons with ischaemic heart disease show a greater platelet mobility in plasma than the controls is not in agreement with the result obtained in the present study In seeking reasons for this disagreement it is to be noted that Hampton makes no reference to the effect of plasma viscosity on the results, the importance of which was clearly evident in the present work

Plasma viscosity values

The plasma viscosity values observed in the present study correspond to the normal values presented in the literature (e.g. Riva 1960, Lawrence 1961, Steel 1963, Fahey et al. 1965, Eastham and Morgan 1965, Somer 1966). The range of plasma viscosity in normal series has generally been reported to be 1.75–2.25. In the present study there was a good correlation between plasma viscosity and fibrinogen content. The study also brought out in patients with CHD a definite tendency to higher plasma viscosity values than those seen in healthy individuals, one of the contributing factors being the higher mean plasma fibrinogen content observed in these patients.

A reduced glucose tolerance was seen more often in the CHD patients than in the control subjects. In their capillary viscometric study Cogan et al. (1961) found the serum viscosity to be 1.75 (S.D. 0.11) in 25 diabetic patients with retinopathy, 1.73 (S.D. 0.12) in 16 diabetic patients without retinopathy, and 1.62 (S.D. 0.02) in 9 normal control subjects. Using rotation viscometer Skovborg et al. (1966) and Ditzel and Skovborg (1968), again, obtained an about 20 per cent higher whole blood viscosity in non-acidotic diabetics than in healthy individuals, whereas no difference was found in the plasma viscosity. Diabetics also had significantly higher alpha$_1$-, alpha$_2$- and beta-globulin fractions and fibrinogen content than healthy individuals. The results of the present study point to the possibility that a disturbance in glucose metabolism manifesting as a glucose tolerance curve of prolonged type may be connected with changes in plasma colloids that increase the viscosity of the plasma.

Of interest is also the observation of a possible correlation between hypertriglyceridaemia and plasma viscosity, which was seen in the series of healthy controls. It may be suggested that the increase in viscosity is due chiefly to large molecular low-density lipoproteins, though their effect on viscosity is markedly lower than that of fibrinogen. They may, however, constitute a minor additional factor in increasing the plasma viscosity also in patients with CHD who are known to have an elevated low-density lipoprotein content as compared with healthy subjects (Besterman 1957, Brown et al. 1965, Gofman et al. 1966, Fredrickson et al. 1967 b).

The observation of increased viscosity in connection with elevated triglyceride values differs to some extent from the result of studies in which experimental or postprandial hypertriglyceridaemia did not cause a change in plasma viscosity (Charm et al. 1963, Konttinen and Somer 1963), even if comparison between the studies cannot be extended to the level of lipoproteins.

When the relationship between the electrophoretic mobility of red cells in plasma and the plasma relative viscosity was analyzed, it was found that correlation was better in the control subjects ($r = -0.87$) than in the CHD patients ($r = -0.57$). A similar difference between the correlation coefficients was observed in the analysis of the relationship between platelet mobility and plasma relative viscosity ($r = -0.64$ and -0.49). However, the S.D. values of cell mobility and plasma viscosity were not much higher in the CHD series than in the control series. The above mentioned differences between the correlation coefficients may point to the possibility that factors regulating cell mobility may be more complicated in patients with CHD and that these patients may have significant biophysical interactions between cells and plasma that are independent of the plasma viscosity, as will be discussed later (p. 34).

THEORETICAL CONSIDERATIONS

In this section an attempt will be made to present certain basic principles in the theory of cell electrophoresis which provide a base for an evaluation of the significance of the results presented above and for discussion of various aspects of cell aggregation and thrombosis in the light of the cell surface charge and plasma factors.

Electrophoretic mobility determining electrical factors of cell surface and suspension medium

Red cells and platelets are at pH values not far removed from neutrality negatively charged due mainly to ionization of the carboxyl groups of N-acetyl neuraminic acid and in the presence of electrolyte they are surrounded by the electrical double layer. When moving in the electrical field the cell will also drag along with itself a thin layer of more or less immobilized water immediately juxtaposed and the slipping plane against the surrounding will thus be located outside the actual cell boundary. The location of this slipping plane determines the magnitude of the electrokinetic or zeta-potential. The reasons for the formation of the slipping plane are complex and influenced by many factors as viscosity, ionic strength and surface roughness.

The motion of the cell in solution caused by an externally applied electrical field is given as the electrophoretic mobility (U) according to Helmholtz (1879) and von Smoluchowski (1921) by:

$$U = \frac{\zeta D}{4 \pi \eta} = \frac{\sigma}{\varkappa \eta}$$

where ζ is the zeta-potential at the surface of shear, η and D are respectively the viscosity and the dielectric constant within the double layer (assumed to be equal to the values for the bulk of the suspension medium), σ is the charge density at the cell surface, $\varkappa$ is the Debye-Hückel constant (dependent on the ionic strength, the absolute temperature and the dielectric constant of the suspension medium).

Thus changes in the electrophoretic mobility might be the result of a change in the surface charge density, a change in the ionic constitution, the dielectric constant or the viscosity of the suspension medium. From the equation above it also follows that the zeta-potential depends on the surface charge density (σ), the ionic constitution and the dielectric constant of the medium.

Details of these formulae have been discussed by Brinton and Lauffer (1959), Lijklema and Overbeek (1961) and Weiss and Woodbridge (1967).

Theoretically it would therefore be possible to calculate from the above equations the surface charge of red cells and platelets; however the application of the equations to a biological system may be too simplified and furthermore it is difficult to determine from plasma the parameters, for instance the dielectric constant, that are needed in addition to the mobility values. For these reasons it was not considered justified in this study to calculate the zeta pontential or the surface charge for either red cells or platelets.

Role of electrical factors in cell contacts

The relationships of the electric factors mentioned above to the suspension stability of cells and to the potential energy barrier between cells have been investigated by Derjaguin and Landau (1941) and Verwey and Overbeek (1948). According to them the total potential energy of interaction (V_T) for a pair of identical spherical particles is given by: $V_T = V_R + V_A$, where V_R means the repulsive potential energy and V_A van der Waal's attractive forces. V_R again may be written as:

$$V_R = \frac{D a \psi^2}{2} \ln [1 + \exp(-\kappa H)]$$

In this equation ψ is the surface potential (assumed to approximate the zeta-potential) a is the radius of a particle, κ is the Debye-Hückel constant, D is the dielectric constant of the suspension medium and H is the minimum distance between the surfaces of the particles. A survey of electrical forces at cell boundaries and of factors that may operate on the repulsion forces has been given by Pethica (1961) Curtis (1962) and Teorell (1965) From these surveys the reader can realize the great complexity of this area.

Experimental research for its part, has attempted to clarify the interrelationship of the cell surface charge and plasma factors to cell aggregation and agglutination by studying the electrophoretic behaviour of cell aggregates, the effect of changes in the cell surface charge on agglutination, and the effect of antibody on the cell surface charge. It has been shown that the electrophoretic mobility of aggregates of red cells, white cells and platelets does not differ from the mobility of single cells (Freundlich and Abramson 1927 Abramson 1965) On the other hand it has been shown that removal of 70–95 per cent of the red cell surface charge by treatment with neuraminidase does not increase agglutination (Brody and Oncley 1965) Contrary to this, antibody may decrease the surface charge of red cells and the decrease is correlated to the agglutinating activity of antiserum, there also exist antibody systems that do not change the surface charge, or the change is dependent on the antiserum concentration (Brody 1954 Sachtleben 1965)

Pollack et al. (1965) have reported that the agglutination of antibody-coated human erythrocytes depends on the zeta-potential at the surface shear and that the enhancing effect of bovine albumin and synthetic polymers on agglutination is related to a decreasing zeta potential as a result of an increasing dielectric constant. Contrary to this suggestion it has been shown theoretically (Brooks et al. 1967) that an increasing dielectric constant does not lead to a lowering of the potential barrier between the cells but rather to an increase

It has recently been shown that the mobility of a red cell variant En (a) deficient in MN blood group antigens is about 40 per cent of normal and that these red cells are agglutinated with incomplete Rh-antibodies in saline. Heterozygous En (a+) red cells have a 10 per cent lower surface charge density than normal cells This results, however in a sufficient decrease of the electrical repulsion between the cells to allow weak agglutination in saline with incomplete Rh-antibodies. A similar behaviour is seen in heterozygous M^k and M^g red cells which also have a diminished surface charge density The zeta potentials agreed well with the borderline value in the measurements of Pollack et al. (cited above) below which agglutination takes place (Furuhjelm et al 1969 Nordling et al. 1969)

In the light of the observations mentioned above, some of the cell agglutination and aggregation phenomena obviously have electrical mechanisms which are connected with the surface charge or with reduction of the zeta potential and which allow the cells to come sufficiently close to each other for the formation of intercellular bonds. Other phenomena, again are governed by non-electrical mechanisms, at least in respects measurable by cell electrophoresis.

Significance of electrical properties of cell surfaces and of plasma in the pathogenesis of coronary heart disease

In the present study no significant difference could be shown between CHD patients and healthy control subjects with respect to the surface charge of red cells or platelets. The results do not, however exclude a possible difference between the two series in the zeta potentials of red cells and platelets owing to dissimilarity of plasma factors. The ionic constitution is hardly of importance in this connection, since the electric conduction values of plasma, which

correlate with the ionic strength did not differ significantly in the two series. Theoretically there may be differences in the plasma dielectric properties owing to dissimilarities in the plasma colloids in the two series (Pollack et al. 1965) such dissimilarities are indicated by the differences in plasma viscosity and fibrinogen content. Unfortunately the direct measurement of the dielectric constant in plasma still seems impossible owing to the polarization effects associated with the high conductance values. An interesting question is what significance beta-lipoproteins have on the plasma dielectric properties and viscosity Coronary disease patients have been shown to have a higher beta-lipoprotein content than healthy individuals (Besterman1957 Brown et al. 1965 Gofman et al. 1966 Fredrickson et al. 1967 b) and a significant positive correlation has been found between the serum viscosity and the beta lipoprotein level in patients with atherosclerosis (Shinagawa 1964) Recently it has been reported that beta-lipoproteins increase significantly ADP and thrombin-induced platelet aggregation and adhesiveness (Farbiszewski and Worowski 1968) one explanation of which may also be changes in the dielectric properties of the suspension fluid

Because thrombosis plays an important role in the development of coronary occlusions, one may question how the electric factors of the cell surface and the plasma can contribute to the formation of a thrombus. It has been shown that damage to the vascular wall (Sawyer and Himmelfarb 1965) as well as advanced atherosclerotic changes (Sawyer et al. 1968) are accompanied by a decrease in the negative zeta potential of the arterial wall which may facilitate the adhesion of platelets to the site of the lesion Platelet adherence to the vascular wall cannot, however be explained on the base of an electrostatic phenomenon alone, but there must without doubt be associated more specific mechanisms that are dependent on the surface properties of platelets, such as protein composition and formation of intercellular bridges. It would be difficult to explain in any other manner why red cells and leucocytes do not adhere to the site of damage. In theory the development of a thrombus can be facilitated also by plasma factors (e g plasma colloids and viscosity) which by reducing either the platelet surface charge or zeta potential diminish the intercellular repulsion and thus may facilitate platelet aggregation Reduction of the zeta-potential should nevertheless be considered also in platelet aggregation, only a partial factor which in combination with non-electrical mechanisms can increase the susceptibility to thrombi.

Alterations in blood viscosity in relation to thrombosis

The patients with coronary heart disease in the present material obviously had an elevated blood viscosity as compared with the control subjects since, firstly the mean plasma viscosity value of the CHD series was above that of the control series and secondly it showed a higher mean level of fibrinogen which promotes reversible aggregation of red cells, especially at low shear rates. An increased blood viscosity again, results in slowing of the blood flow which may lead to local hypoxia and also to possible occlusion of an arteriolar lumen by a red cell aggregate, and the hypoxia may give rise to endothelial damage. Slowing of the circulation, on the other hand will cause the platelets in suspension to be less concentrated coaxially and they drift to the peripheral layers of the flow which in turn increases the risk of platelet adhesion (Dintenfass et al. 1966) The risk can be increased also by ADP and ATP released as a result of endothelial damage and of possible local haemolysis (Eastham 1966) ADP has been shown to cause increased platelet aggregation in concentrations that also reduce electrophoretic mobility of platelets (Hampton et al. 1967 Betts et al. 1968 Gröttum 1968, Rutty and Vine 1969) One explanation of this phenomenon can be a decreased electrical repulsion between the cells. Thus increased viscosity as a rheological factor may be linked by a number of mechanisms to the series of events that participate in the formation of a local thrombus.

SUMMARY

The purpose of the present study was to investigate the surface charge of red cells and platelets in patients with coronary heart disease and in healthy control subjects by means of the cell electrophoresis technique. Plasma viscosity determinations were made with a capillary viscometer. The blood samples were obtained from 55 patients with coronary heart disease and 48 healthy control persons.

The red cells of the coronary heart disease patients moved more slowly in plasma than those of the healthy controls, but after the viscosity correction there no longer was a statistically significant difference in the electrophoretic mobilities of the two series. The mobilities in phosphate buffer solution in the two series did not differ from each other.

The mobility of the platelets of the coronary disease patients was also slower than that of the control subjects, but after the viscosity correction there was no difference in the surface charge of platelets in the two series.

The relationship between the cell mobility in plasma and the plasma relative viscosity was better in the control subjects than in the coronary heart disease patients. This may point to the possibility that plasma factors which determine cell mobility are more complicated in coronary heart disease patients than in healthy subjects, and that factors other than plasma viscosity may have a role in biophysical interactions between cells and plasma in coronary patients.

The plasma viscosity in the coronary heart disease patients was higher on the average than in the healthy control subjects. The plasma fibrinogen concentration in coronary patients was statistically significantly higher than that in the control subjects. A good positive correlation was evident between plasma viscosity and fibrinogen content in both series although the correlation was stronger in the healthy subjects. No correlation was found between the cholesterol content and the viscosity of plasma but on the other hand a correlation was seen in the control series between elevated triglyceride values and plasma viscosity when the viscosity values in the highest quartile of triglycerides were compared with the values in the lowest quartile. Patients whose glucose tolerance curve was of the prolonged type as a sign of reduced glucose tolerance had a significantly higher mean plasma viscosity than the remainder of the CHD series.

The possible effect of increased plasma viscosity on the rheological properties of the blood and its relation to the formation of thrombi is discussed. The electrical properties of blood cells and plasma in regard to suspension stability and coronary heart disease are discussed. On the basis of the present study it seems obvious that there are no significant differences on the surface of red cells or platelets in coronary patients as compared with healthy persons, but differences are more likely to be found in plasma and serum factors.

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Supplementum 508

Studies on Idiopathic Non-tropical Sprue

The familial occurrence of sprue
Relationship between sprue and megaloblastic anaemia of pregnancy and puerperium
The significance of partial gastrectomy for manifestation of symptoms

By Börje Ek

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The familial occurrence of sprue. Relationship between sprue and megaloblastic anaemia of pregnancy and puerperium. The significance of partial gastrectomy for manifestation of symptoms

by

BÖRJE EK

CENTRALTRYCKERIET [illegible]

CONTENTS

STUDIES ON IDIOPATHIC NON TROPICAL SPRUE

by Börje Ek

CORRIGENDA

P 9r lin 3 should read
peptidases has been described by Berg et al (pers. comm.)

P 11 line 23 should read
mechanism. Normal activity of dipep-

P 11 line 23 should read
Messer et al. (1961) and diminished by Lindberg et al. (1968)

P 13 line 15 should read
bone marrow changes (Dawson 1962 among others). The

P 21 line 7 should read
jugation (Donaldson 1965). 6) Liver damage

P 21 line 33 should read
maintained that small intestine changes after

P 23 line 35 should read
180—1000 pg per ml

P 26, Table 6
Patient C was diagnosed 1950

P 34r line 2 should read
the right

P 39r line 5 should read
lies on or above the mean average of the

P 41 the equation should read

$$\text{Deviation points} = 50 \quad \frac{SF \quad M_c}{SD_c}$$

P 42r line 2 should read
serum. No correlation could be proved in the controls.

P 45 in the Fig. text
during the period 1952—1961

P 47 in the heading of the Table 13
The relative frequency in per cent of

P 50r lines 30—33 should read
average mean with a significance of $p < 0.005$

P 53 in Table 21
Signum OK should read DK
Signum RH and HK should both have the mark 1 under the column $p \leq 0.001$

P 54 line 10 should read
and the population in the respective

P 60, line 21 should read
this discussion, that 5 out of 9 families dif

I INTRODUCTION

During the period 1952—1965 twenty patients with the diagnosis idiopathic sprue underwent treatment at the medical clinic of Umeå Hospital. Ten of these patients were women and two of them had had megaloblastic anaemia of pregnancy and puerperium. Nine of the twenty patients had undergone partial gastrectomy—in eight cases because of peptic ulcer in the duodenum or stomach and in one case because of a gastric polypus.

The high frequency of megaloblastic anaemia of pregnancy and earlier gastrectomy in the above-mentioned material is remarkable, and hints at the possibility of a connection between idiopathic sprue and both megaloblastic anaemia of pregnancy and partial gastrectomy

These observations gave rise to the following study the aim of which it has been to examine the possible connection between idiopathic sprue and both megaloblastic anaemia of pregnancy and partial gastrectomy In practically all sprue material it is debatable whether the diagnosis in each single case is satisfactorily supported. This also applies to the author's material not least those patients who have undergone earlier partial gastrectomy It is known that an increased occurrence of sprue has been proved among relatives of children with celiac disease. The author has studied the occurrence of sprue among the relatives of his sprue patients with the aim of possibly being able to demonstrate a familial occurrence of sprue, and to confirm the sprue diagnosis of the primary material by possible proving that the disease occurs in relatives of the patients.

This study with the above-mentioned aim has been drawn up along the following lines

1) Investigation into the occurrence of signs of sprue in relatives of the author's sprue patients including those in the above-mentioned sprue material who underwent gastrectomy
2) Analysis of the frequency of diagnosed idiopathic non tropical sprue diagnosed megaloblastic anaemia of pregnancy and puerperium and partial gastrectomies performed in Sweden and the county of Västerbotten.
3) Analysis of the occurrence of megaloblastic anaemia of pregnancy and puerperium among sprue patients in Sweden
4) Investigation into the occurrence of sprue symptoms in patients with earlier megaloblastic anaemia of pregnancy and puerperium.

Parallel with the investigations dealt with in 1 and 4 a control material selected at random was examined, which concerning sex and age corresponded with the relative and patient material.

Ad 1 The author expects to be able to throw light on the question of the familial occurrence of sprue. As far as the author has been able to find out, this question has not previously been dealt with on the basis of adult index cases and with control material. Existing investigations may be characterised as rather incomplete (Table 2)

Ad 2. By analysing how often one can reasonably expect to find the combination sprue and partial gastrectomy the author expects to be able to show whether the observed simultaneous occurrence of the above conditions is due to coincidence or not, and

to be able to analyse the said occurrence, in the event that it has not come about merely by chance

Ad 2—4 The investigation of a sufficiently large material of female sprue patients with regard to the occurrence of earlier megaloblastic anaemia of pregnancy and puerperium, and the investigation of women with earlier megaloblastic anaemia of pregnancy and puerperium with regard to the occurrence of sprue signs, is expected to show a possible connection between these conditions.

Preliminary results of these investigations have previously been published by the author (Ek 1966, 1967 and 1969)

Table 1 Names of diseases with general idiopathic intestinal malabsorption

A. *From tropical and subtropical zones*			
Inlandse Sprouw	East Indies	Ten Rhinje	1687
Aphtoides chronica	Barbados	Hillary	1759
Indische sprouw	Malayan archipelago	Bosch	1837
Sprue	China and elsewhere	Manson	1880
Psilos	Manilla and elsewhere	Thin	1882
B. *From temperate zones*			
Belgarum Sprouw	Netherlands	Ketelaer	1669
Coeliac affection	England	Gee	1888
Intestinal infantilism	USA	Herter	1908
Coeliac disease	England	Miller et al.	1920
Nicht Trophischen Sprue	Denmark	Hess Thaysen	1926
Idiopathic Steatorrhoea	"	"	1929
Idiopatische Sprue	Germany	Adlersberg	1955
Adult celiac disease	England	Cooke	1962
Celiac sprue	USA	Rubin	1961
Coeliac syndrome	England	Hindle & Creamer	1965

II HISTORICAL SURVEY

Sprue

The clinical picture of a chronic, afebrile and often intermittently appearing intestinal disease with excretory disorders, signs of general malabsorption and more specific deficiency conditions has long existed under many different names (Table 1) The disease was already known in ancient times, judging from descriptions by Charaka, about 1500 B C. (cf Baker 1968), and Aretaeus, about 150 B C. (cf Badenoch 1960). The term sprue has its origin in the word sprouw which was used by Ketelaer (1669) as the namn for a disease observed in the Nether lands and characterised by massive bowel evacuations and aphtous changes in the mucous membrane of the mouth. A complete distinct description of a malabsorption condition, observed in the West Indian archipelago was published by Hillary (1759) In 1880, in dependent of each other van der Burg and Manson carried out observations and investigations of a large number of malabsorption cases in the Far East. On the basis of these studies the disease, since then most commonly known as tropical sprue, could be defined. Gee (1888) described a similar disease, observed in infants in England. The disease, called "coeliac affection could according to Gee even afflict adults in rare cases. Neither children nor adults with this disease had visited the tropics. Gee's description of the disease was forgotten. The disease in children was rediscovered by Schütz (1905) Herter (1908) and Heubner (1909), and in time became known by the name coeliac disease (Miller et al. 1920) During the first decades of the twentieth century occasional casuistic reports were published of cases of sprue which appeared in the temperate zones. First to describe the disease of sprue from Europe after Ketelaer was, as far as is known, Richartz (1905) (cf Hess Thaysen 1932), and the first description from North America was published by Graham (1905) (cf Wood 1915) In Sweden the first case of sprue was published by Engel in 1931 The first closer studies of the disease of sprue in non-tropical areas were made by Hess Thaysen (1926) Holmes & Starr (1929) and Bennett et al (193?). Hess Thaysen (1932) combined his own and previously published cases of non tropical sprue and observed, among other things, that some adults with non-tropical sprue had had symptoms even when they were children, that the signs and symptoms of non-tropical sprue closely agreed with that of tropical sprue, and that changes of the small intestine were not present if postmortal autolysis was prevented with for malin immediately after death took place. Hess Thaysen asserted that tropical sprue and non tropical sprue in adults, and coeliac disease in children were closely related, probably identical disease conditions of unknown etiology characterised by distinctive symptoms such as fatty diarrhoea, loss of weight, meteorism, anaemia, tetany oedema and aphthous stomatitis in the absence of specific pathologically anatomic changes in the small intestine. Hess Thaysen observed that these patients had a flat glycose tolerance curve. Hess Thaysen combined, as previously mentioned, tropical sprue, non-tropical sprue and coeliac disease of childhood and used the common term idiopathic steatorrhoea. He distinguished between this disease and other forms of steatorrhoea in for example pancreas diseases (Bright 1833), disturbed gall secretion (Müller 1888) tabes (cf Hess Thaysen 1932), amyloidosis (cf Hess Thaysen 1932), morbus Basedow (Faller 1910) gastrentero-stomia (Hess Thaysen 1932). Some authors believed doubtfully the view that besides certain outward similarities there was

some connection between tropical sprue on the one hand and coeliac disease of childhood and non-tropical sprue on the other (Miller 1926 Bennett et al. 1932) In England, above all idiopathic steatorrhoea came to mean the same as non tropical sprue or idiopathic sprue.

The pathological changes of the small intestinal mucosa observed earlier at autopsies of sprue patients by among others, Beneke (1910) Justi (1913), Manson-Bahr (1915) and Mackie & Fairley (1929) were considered by Hess Thaysen to be secondary to postmortal autolysis. The current opinion after Hess Thaysen that idiopathic steatorrhoea lacked histological support had to be modified in time. Milanes et al. (1951) and Paulley (1957) were able to prove with histological techniques in tropical sprue and idiopathic steatorrhoea mucosal changes in specimens of small intestine which were excised as samples in connection with laparotomy Closer examination of mucous membrane from the small intestine could be carried out more generally only when the methods for peroral biopsy had been developed (Shiner 1956 Crosby & Kugler 1957 and others) Characteristic histological changes of the mucosa in the lower part of the duodenum and the upper part of the jejunum in idiopathic steatorrhoea, coeliac disease of childhood and tropical sprue were demonstrated by Doniach & Shiner (1957) Butterworth & Perez Santiago (1958) Rubin et al. (1960 a), Fone et al. (1960) and others. These findings have since been confirmed in several investigations. A valuable complement to the histological examination of the small intestine mucosa is the scrutiny of the mucosa under dissection microscope (Holmes et al. 1961) In sprue, the changed villi are grouped according to their shape as leaf-like and ridge-like, according to the degree of deviation from the normal finger like. These are considered moderately severe changes and correspond to an imagined flattening, broadening and shortening f the individual villi In more severe changes of the villi the intestinal mucosa takes on an appearance reminiscent of brain convolutions usually called convolutiones, or a completely erased structureless appearance—so-called flat mucosa with or without mosaic pattern. These changes, observable under the dissection microscope, correspond histologically by and large to a gradual reduction of the villus layer of the intestinal mucosa, transformation of the mucosal epithelium from cylindrically regular to cubically irregular increase of the gland layer of the mucosa, increasing tortuosity of the glands, increasing mitosis frequency in the cells of the glandular layer and increasing plasmocellular cell infiltration of the lamina propria. Quite varied terminology has been used to describe the morphological changes. According to Shiner and Rubin, the above-described severe changes in the intestinal mucosa, corresponding to flat mucosa, are called "subtotal villous atrophy" and "severe to moderate celiac sprue specific abnormalities" respectively the above-described moderately severe changes in the intestinal mucosa, corresponding to a mucosa with ridges or convolutiones, are called "partial villous atrophy" and "moderate to mild celiac sprue specific abnormalities" respectively

Different authors have different criteria for a morphologically normal intestinal mucosa. Small intestine changes which in the West would be considered as clearly deviating from the normal have, for example, been observed in asymptomatic persons in Thailand (Sprinz et al. 1962), India (Baker et al. 1962), East Pakistan (Lindenbaum et al. 1966), West Pakistan (Russel et al. 1966) Singapore (England & O'Brien 1966) Haiti (Klipstein et al. 1966) and other places. Different genetic and environmentally conditioned factors in the morphological formation of the intestinal mucosa have been suggested as an explanation of these morphological variations. Reduced lactase activity of the mucosa has been demonstrated by McMichael et al. (1965), who maintained that the reduction could be genetically conditioned.

The above-described morphological changes in the intestinal mucosa usually located in the

upper part of the jejunum have been considered specifically diagnostic for celiac sprue (Shiner et al. 1960 Rubin et al. 1961 Benson et al 1964 and others) Several authors have however described similar small intestinal changes in other diseases also such as malignant lymfom (Gough et al. 1962 and others) sarcoidos (Gjone et al. 1965 among others), ulcerative colitis (Salem et al. 1964) hookworm disease (Sheehy et al. 1962 and others) giardia lamblia (Yardley et al. 1964 among others) regional enteritis (Shiner & Drury 1962), hypogammaglobulinaemia (Pelkonen et al 1963 among others) (cf Collins 1965 Rubin & Dobbins 1965 and others). The specificity of the changes in the small intestinal mucosa has therefore been questioned. Some authors have described cases of idiopathic sprue where it has not been possible to demonstrate definite morphological deviations of the small intestinal mucosa (Thurlbeck et al. 1960 Fone et al. 1960 Girdwood et al 1961 Patnaik 1967) In some of these negative cases a re-examination of the intestinal mucosa has shown clearly deviating changes (Girdwood 1966) In others, an electron microscopic examination revealed microvilli changes of that type which are believed to be found in celiac disease (Patnaik 1967) Not much is known about the frequency of negative biopsy findings in celiac disease, nor can it be definitely estimated on the basis of published material on the disease. Although most authors demand demonstrable severe changes of the small intestinal mucosa for the diagnosis celiac disease.

According to many authors the morphology of the small intestinal mucosa in celiac disease are poorly correlated to both the clinical course of the disease and its degree of severity and to the results of biochemical function test (Thurlbeck et al 1960 Rubin et al. 1960 b Samloff et al. 1964 McGuigan et al. 1964 McDonald et al. 1965 among others) Myhren et al. (1965) observed however a fairly good correlation between the morphological appearance of the small intestinal mucosa and the succinate dehydrogenase activity Good correlation between the morphology of the small intestinal mucosa and the activity of di peptidases has been described by Lindberg et al (1968).

The pathological changes of the small intestinal mucosa observed in tropical sprue are according to some investigators (cf Ménéndez-Corrada 1968) rarely as severe as those found in celiac disease.

Very early certain kinds of food were considered to have a significance for symptoms of idiopathic sprue This opinion was usually founded on empirically-gained experiences from treatment trials with diets (cf Hansen & Staa 1936)—e.g. milk diet (Manson 1925) low fat food (Hess Thaysen 1932) all-meat diet (Cantlie 1936), banana diet (Haas 1924) protein rich, low fat and low-carbohydrate food (Fairley 1934) Dicke (1950) found that children with celiac disease quickly became symptom free and began to regain their normal height increase after wheat, rye and barley had been eliminated from their diet. Later Dicke et al (1954) were able to isolate the harmful ingredient in wheat flour and demonstrate that it also existed in the protein fraction, called gluten. A gluten free diet proved to be of great importance in the treatment of celiac disease of childhood and also in non-tropical sprue n adults (Ruffin et al 1954 French et al 1957 and others)

The beneficial effect of a gluten free diet in treating tropical sprue is considered less pronounced (Ansenjo et al 1958 Sprinz et al. 1962) The response to treatment with gluten-free diet, which is usually judged on the basis of clinical biochemical and histopathological criteria, can in individual cases show great variation. Gluten is commonly supported to play an important role in the formation of small intestine lesions in celiac disease. A clinical improvement from the treatment with gluten-free diet is not always followed by a histological or biochemical normalisation (Bayless et al. 1963 Bolt et al. 1964 Ruffin et al. 1964 among others) Complete lack of response to treatment trials

T bl In estigations i t the familial occurrence f celiac disease and idiopathic sprue.

Numbe t inde cases	Diagnosis	Basis for di gnosis i rel ti	N mber of rel ti es examined	Relationship	Number of rel ti es w th the disease	Relat e f equency		A thor
130 child en	Celiac dise se	(1) (2) a. namnesis b. steatorrhoea	Not stated	Not tated		9.2		Davidso et l (1950)
5 adults	Idiopathic steatorrhoea	(1) (2) a. anamnesis b. steatorrhoea	Not stated	Not stated		4		Da idson et al (1950)
104 hildren	Celiac disease	mnesis	117 189 36	siblings parents grandparents	15 11 4	12 8 / 5.8 1 1	4.6	Thompson (1951)
50 hildren	Celiac disease	anamnesis	59 100	siblings parents	5 5	8.5 / 5.0 /	6.3	Boyer & Andersen (1956)
88 children	Celiac disease	a. hospital diagnoses b. steatorrhoea	205 85 589 806	siblings parents grandparents ousins	5 2 1 1	2.4 / 2.3 / 0.2 / 0.1 /	0.5 /	Carter et al (1959)
2 children 2 adolescent 13 adult	Celiac sprue	(2) Severe hanges f small intestine shown by histological ex mination	34 33 17 21	parents siblings hildren nephew and leces	0 5 2 4	 15 % 11.8 / 19 /	10.5 /	MacDonald et al. (1965)

(1) I formation on relati es condition was bt ined hrough writing t the doc who treated th relati in question. The i formatio on steatorrhoea was gi en by the docto in question.
(2) Con rol material is lacking. Determ nations f faecal fat ha not been mad by a un tary method.

with gluten free diet, or relapses while initially successful treatment with gluten free food is in progress, are reported as occurring in up to 30 /• of treated and are more usual in adults than in children (French et al 1957 Hindle & Creamer 1965 Pink & Creamer 1967) Sometimes some cases, resistant to treatment with gluten-free food, can respond to other elimination diets where, for example, milk, eggs, etc. are excluded (Taylor et al. 1961 Collins and Isselbacher 1964 Cooke 1968).

The connection between the gluten content of food and the small intestinal lesion in celiac disease is not known. It has been assumed that in celiac disease the small intestinal mucosa, deficient in certain enzymes like dipeptidases, lacks the normal ability to digest gluten (Krainick et al. 1959 Frazer 1962 and others) Incompletely digests of gluten were believed to achieve their harmful effect on the intestine by means of a toxic or allergic mechanism. Diminished activity of dipeptidases in celiac disease has been described by Messer et al. (1961) and Lindberg et al. (1968) However after improvement from a gluten free diet, the previously diminished activity of dipeptidases is restored to normal (Lindberg *et al.* 1968) *which would seem to in*dicate that the demonstrated enzyme deficiency is secondary to the small intestinal lesion

The majority of authors consider that celiac disease in children and idiopathic steatorrhoea in adult are in principle the same disease. As support for this view it is stated for example, that patients with idiopathic steatorrhoea have not infrequently had symptoms even in childhood (Hess Thaysen 1932 Bennett et al. 1937 Davidson & Fountain 1950 Cooke et al. 1953) that children with celiac disease often have older relatives with idiopathic steatorrhoea (Table 2) and that both children with celiac disease and adults with idiopathic steatorrhoea usually have characteristic and similar histological changes of the small intestinal mucosa (Shiner 1956 Rubin et al. 1960 a) which most often display a favourable therapeutic response to a diet where gluten has been eliminated.

The question of whether tropical sprue and idiopathic non tropical sprue are the same disease is controversial. Many authors believe them to be two separate diseases, and bring forward as arguments, inter alia, dissimilarities in symptomatology clinical course, geographical distribution and therapeutic response to gluten-free food. It has further been stated that the histological changes of the small intestinal mucosa are less pronounced in tropical than non-tropical sprue. Similarities between both diseases have been proved, however—for example that both tropical and non-tropical sprue primarily afflict fair skinned people often with blood-group 0, and show similar morphological changes in the small intestinal mucosa with secondary enzyme-deficiency symptoms and steatorrhoea, etc. (cf Ménéndez-Corrada 1968).

The question of the familial occurrence of celiac disease and idiopathic sprue has been dealt with in greater detail by Davidson et al. (1950) Thompson (1951) Boyer & Andersen (1956), Carter et al (1958) and McDonald et al. (1965). Table 2 shows the results of these authors investigations. On the *basis of the results from questions about* possible sprue symptoms, information on definite hospital diagnoses or the results of biopsy of the small intestine, these authors maintained that 0 1—19 of the patients relatives have celiac disease or idiopathic steatorrhoea. From Table 2 it can be seen that only Davidson and colleagues and McDonald and colleagues have based their studies on adult material Those results Davidson and colleagues present are based on second-hand information about diagnoses and demonstrated steatorrhoea, obtained by means of questions to consulting doctors. McDonald and colleagues use as their basis the results of biopsy of small intestine of relatives of adults and children with gluten enteropathy and defined histological changes in the small intestinal mucosa. There is no account of matched control material in this investigation.

Published studies on the familial occurrence of celiac disease and idiopathic steatorrhoea have not committed themselves on the question of a possible hereditary trait. The possibility of a single autosomal and dominant gene with incomplete penetration has been discussed by Andersen & Di Sant Agnese (1953) Thompson (1951) and McDonald et al (1965), among others. Davidson et al (1950) believed they had found evidence for the existence of single recessive autosomal hereditary trait. McConnel (1966) on the basis of information available in literature about the familial occurrence of celiac disease and idiopathic sprue, suggest that a polygenetic hereditary trait may be considered most likely

Megaloblastic anaemia of pregnancy and puerperium

Severe anaemia conditions in connection with pregnancy were described by several authors as early as the middle of the 19th century (Channing 1842 Lebert 1853 Gusserow 1871 and others) When describing "pernicious progressive anaemia" Biermer (1872) noted that he had observed forms of the disease which first appeared in connection with pregnancy Schmidt (1918) and Osler (1919) showed that megaloblastic anaemia of pregnancy differed from genuine pernicious anaemia in that it healed Filo (1931) observed that, in contrast to genuine pernicious anaemia there was usually no achlorhydria in cases of megaloblastic anaemia of pregnancy The earliest published material on megaloblastic anaemia of pregnancy came from Scotland (Stevenson 1936, 1938 Davidson et al 194_), Sweden (Abramson 1938 Segerdahl 1941) and England (Miller & Studdert 194? Lescher 194 Callender 1944). The changes in cases of megaloblast anaemia of pregnancy are rarely as pronounced as those in cases of genuine pernicious anaemia.

Patients with megaloblastic anaemia of pregnancy responded n ery different ways to liver therapy Some cases responded excellently to liver therap (Brault 1978 and others), while in other cases there was complete or partial lack of response (Meaker & Borgiono 1929 and others) Good therapy results were obtained from peroral treatment with folic acid (Moore et al 1945 Spies 1946 Davidson et al. 1948). In a material comprising cases of megaloblastic anaemia of pregnancy Thompson & Ungeley (1951) reported on the results of treatment with different liver preparations, folic acid, vitamin B_{12} and autolysed yeast. The response to the treatment, judged on the basis of reticulocyte and erythrocyte increase, varied considerably according to each preparation. Highly favourable treatment effects were obtained from peroral administration of folic acid, dried liver and yeast extract. Moderately favourable effects were obtained from parenteral administration of low-grade purified liver extract and autolysed yeast. The effect of the latter preparations is due to their probable folic acid content. Parenteral administration of vitamin B_1 and high-grade purified liver extract, probably due to the content of vitamin B_{12}, produced only very slight effects or none at all. Complete absence of response to vitamin B_{12} treatment has been described by Bethell et al (1948) Day et al. (1949) and Davidson et al. (1948) and others. The favourable effect of vitamin B_{12} therapy reported by Nieweg et al. (1954), Moore et al. (1955) Badenoch et al (1955) and Killander (1958), is ascribable to very large doses of vitamin B_{12}.

In large doses folic acid as well as vitamin B_{12} seem to be able to cause the megaloblastic blood changes into remission (Schrumf 1950 195 Vilter et al. 1950 and others). To be able to verify a definite maturity factor deficiency therapeutic tests should therefore be carried out with small doses of the maturity factor in question (Marshall & Jandle 1960 Hansen & Weinfeldt 196?)

Microbiological determinations of folic acid and vitamin B_{12} have proved to be most valuable in the differential diagnosis of megaloblastic anaemias. Low content of blood folates have been constantly observed in patients with megaloblastic anaemia of pregnancy Nevertheless healthy non anaemic

pregnant women not infrequently show lower levels of serum folates and vitamin B_{12} than non-pregnant women of fertile age (Hansen 1959 Solomons et al. 1962 Streiff & Little 1967 Heinrich 1954 Spray & Witts 1958) Pregnant women with megaloblastic anaemia of pregnancy usually show still lower levels of serum folates (Hansen 1964 Izak et al 1961) The average low level of serum folates and vitamin B_{12} in serum during uncomplicated pregnancy has been the subject of different interpretations. Ball & Giles (1964) and Hansen (1964) consider this reduction of maturity factors in the blood of non anaemic pregnant women to be a normal physiological phenomenon Even patients with megaloblastic anaemia of pregnancy can have a low vitamin B_{12} content in serum. Usually the low vitamin B_{12} values of serum are normalised after adequate treatment of the anaemia with folic acid (Ball & Giles 1964)

Megaloblastic anaemia of pregnancy is usually defined as a megaloblastic often severe anaemia during pregnancy determined by folic acid deficiency The criteria for folic acid deficiency however vary according to different authors, as does opinion over which laboratory examinations best mirror the folic acid metabolism. With the support of different investigations some authors have claimed that a latent folic acid deficiency is common during pregnancy In these cases they usually refer to folic acid clearance (Chanarin et al. 1958) folic acid assay of the blood (Toennies et al 1956 Hansen 1959 Grossowicz et al. 1960 Baker et al 1960 and others) the FIGLu test (Luhby et al. 1960 Hibbard 1962) and blood and bone marrow changes (Dawson 1962) The reliability of these determination methods for measuring folic acid deficiency have been discussed by among others, Girdwood & Delamore 1961 Hansen 1964 Ball & Giles 1964 Spray & Witts 1958, Chanarin et al. 1963 Normal values can be expected during pregnancy that are different from those of non-pregnant women of similar age (Ball & Giles 1964 Hansen 1964 among others). The

Table 3 The incidence of megaloblastic anaemia in pregnancy

No. of confinements	Frequency in per cent	Centre	Author	
8,000	0.2	Edinburgh	Davidson et al.	1942
3 482	0 49	Glasgow	Scott	1954
10 623	0 17	Canada	Lowenstein et al.	1955
2,700	0.52	Liverpool	Forshaw et al	1957
3 199	2.8	N Staffordshire	Giles & Shuttleworth	1958
	4.2	Dublin	Hourihane et al.	1960
	3.6	Sunderland	MacKenzie & Abbott	1960
10 629	1 09	Yorkshire	Ainley	1961
40,000	0.05	Dallas	Pritchard	1962
841	7.0	Manchester	Dawson et al.	1962
3 000	0 43	Marburg an der Lahn	Huber & Schlagter	1963
	14	New York	Luhby	1963
23 000	0.087	Gothenburg, Sweden	Hansen	1964
2,685	2.35	Montreal	Lowenstein et al	1966

morphological changes in maturity factor deficiency have been judged somewhat differently by different authors on bone marrow examination. This applies above all to the evaluation of early and relatively unspecific signs of maturity factor deficiency such as the solitary and scarcely extensive appearance of macro-granulocytic changes in the myelopoesis. Such changes are relatively common towards the end of pregnancy but without any definite connection with maturity factor deficiency and not infrequently in combination with iron deficiency (Lowenstein et al. 1962 Hansen 1964).

There is a great variety of information about the frequency of megaloblastic anaemia of pregnancy Reports of morbidity in temperate zones give frequency figures of between 0 1 and 14 / (cf Table 3). It should, *however be noticed that different investigators* have had different diagnosis criteria. Hansens (1964) report refers to women in Göteborg.

Hansen suggests that for a definite diagnosis of megaloblastic anaemia of pregnancy the following diagnostic criteria should be met presence of anaemia neither completely nor partially caused by iron deficiency megaloblastic erythropoesis low blood folates compared with healthy pregnant women, and therapeutic response to small doses of pteroyl glutamic acid within the range, for example, 0.2—0 4 mg per day With largely the above requirements for diagnosis Hansen (1964) found on the basis of information from literature, that the frequency of megaloblastic anaemia of pregnancy was very similar in different parts of the Western hemisphere.

Several different causes of megaloblastic anaemia of pregnancy have been discussed. Thus insufficient supply increased need, deteriorated absorption and also constitutional factors possibly in the form of a primary defect in the folic acid metabolism have been given as reasons for the occurrence of folic acid deficiency

Insufficient supply of folic acid has been considered to originate from a diet low in meat and vegetables (Clarke et al 1954 and others) or from food deprived of its folic acid content through preparation (Herbert 1963 Hibbard & Hibbard 1963 and others), or through reduced intake of food because of molimina, glossitis, etc. Thompson (1957) believed she found an increased frequency of megaloblastic anaemia of pregnancy during the winter months, and she related this situation to the lower folic acid content of food at that time of year

Increased need of folic acid has been considered to arise through, among other things, the need of the growing foetus for folic acid (Chanarin et al. 1959) Thus the frequency of megaloblastic anaemia is increased among multiparae (Thompson & Ungley 1951 Scott 1957 and others) and among women with twin pregnancies (Chanarin et al 1959 Gatenby & Lillie 1960 and others)

Reduced absorption of folic acid during pregnancy has been described by Chanarin et al. (1959) among others. Girdwood & Delamore (1961) found low folic acid levels in serum in healthy pregnant women after peroral administration of pteroyl-glutamic acid. Layrisse et al (1960) found that twelve out of fourteen women with megaloblastic anaemia of pregnancy had deteriorated absorption of pteroyl-glutamic acid and in most cases the absorption was not normalised even though the anaemia was cured Hansen (1964) showed that of six examined women with megaloblastic anaemia of pregnancy two had pathological values and reduced absorption of folic acid, two had sub-normal values and two had low normal values on absorption examination with pteroyl-glutamic acid. Hansen attached no value to the possible folic acid malabsorption, but assumed that megaloblastic anaemia of pregnancy was caused by a deteriorated folic acid metabolism

The fact that some women show a tendency to suffer a relapse, argues in favour of constitutional factors in the development of megaloblastic anaemia of pregnancy Relapses of megaloblastic anaemia in some non-pregnant women have also been reported. Predisposing constitutional causes of megalo-

blastic anaemia of pregnancy have been discussed by among others, Schmidt (1918) Miller et al (1942) and Callender (1944) who believe they have found evidence of familial occurrence of megaloblastic anaemia of pregnancy Giles et al. (1960) and Ainley (1961) gave an increased frequency of blood-group A among these patients as support for the view that megaloblastic anaemia of pregnancy can be constitutionally determined. Hansen (1964) assumed that megaloblastic anaemia of pregnancy was caused by a primary constitutional defect in the folic acid metabolism. In a check-up of women who 1—10 years earlier had had megaloblastic anemia of pregnancy Hansen found that seventeen out of eighteen women examined still had signs of folic acid deficiency Since, however only a few of them showed low values in serum after peroral administration of folic acid, a reduced folic acid absorption was not assumed to be the pathogenetic mechanism. Further support for the view that predisposing constitutional factors can be of significance in the development of megaloblastic anaemia of pregnancy has been given by Temperley et al. (1968) in a prospective examination he was able to show that all women who had had low blood folates in the initial pregnancy period developed megaloblastic anaemia later during pregnancy

Further reasons for the development of folic acid deficiency symptoms have been discussed. Vitale (1966) observed that iron deficiency can result in reduced utilisation of folic acid.

The appearance of a genuine pernicious anaemia during pregnancy is considered an extreme rarity Ball and Giles (1964) and Hibbard & Hibbard (1968) among 18 000 and 30 000 examined pregnant women respectively were not able to find one single case Hibbard (1962) reported that of 12,000 pregnant women two adequately treated women with known genuine pernicious anaemia had undergone normal uncomplicated deliveries. Similar isolated cases have been reported earlier (cf Adams 1958) Untreated genuine pernicious anaemia is considered to cause sterility (Lillie 1962 Sharp et al 196? Jackson et al. 1967 Hall 1968) Cases of genuine pernicious anaemia diagnosed during pregnancy are mentioned but not described in detail by Varadi (1964), Girdwood (1966) Fisher & Taylor (1967) and others. Armstrong et al (1968) described two patients who developed a genuine pernicious anaemia during pregnancy

Table 4 lists works which deal with possible connections between sprue and pregnancy and sprue and megaloblastic anaemia of pregnancy The question of steatorrhoea in pregnant women with megaloblastic anaemia of pregnancy has been dealt with by Badenoch et al. (1955), Moore et al. (1955) and Giles (1958 1966) Badenoch and Moore found a normal fat balance in some examined patients with megaloblastic anaemia of pregnancy Giles & Shuttleworth (1958) observed that steatorrhoea existed in about 20 % of the examined pregnant women with megaloblastic anaemia of pregnancy In 1966 Giles observed that on examination of 85 pregnant women with megaloblastic anaemia and 27 healthy pregnant women 18 and 1 respectively had a fat content in faeces exceeding 6 g per day and three out of six women who suffered a relapse of megaloblastic anaemia unconnected with pregnancy had steatorrhoea.

From the summary in Table 4 it is apparent that a number of authors have described tropical sprue as often making its first appearance during the final stages of a pregnancy It has been maintained that the sprue-condition is provoked or aggravated by folic acid deficiency during pregnancy Cases of idiopathic sprue which first appeared or were aggravated during pregnancy or puerperium have also been described. It appears, furthermore, that in isolated cases the combination idiopathic sprue or tropical sprue and megaloblastic anaemia of pregnancy has been observed. There has been no systematic investigation of patients with megaloblastic anaemia of pregnancy with regard to sprue symptoms. An increased frequency of

T bl 4 Works on the possible connection between sprue and pregnancy and sprue and megaloblastic anaemia of pregnancy

Malabsorption dise se	Megalobl stic anaemia of pregnancy	Possible connection	Author
T opical sprue		F rst appearance often during pregnancy	Manson (188C) d. Burg (188"), Krjukoff (1927), Manson-Bahr (193"), Jones (1939)
	1 case	Sprue symptoms first ppe red during puer perium when steatorrhoea and flat glycose toleranc curv were demonstrated.	Mogensen (1936)
One case f idiopathic st atorrhoea		Symptoms first appeared d ring puerperium when megaloblastic anaemia was demonstra ed	H nes & McBryde (1936)
One case of idiop thic st orrhoea		Symptom first ppeared during puerperium etany macrocytic naemia and steatorr hoea late developed.	Nussbrecher & Morton et l. (1937), Benett & Hardwick (194C)
T o cases of non-tropical sprue		Symptoms first ppeared during pregnancy with dev lopment of megaloblastic an emia	M rkoff (1938)
	1 case	Sprue symptom first ppeared during puerperium w th naemia and steatorrhoea.	D idson (1948)
	1 case	Sprue symptoms first ppeared during puer peri m when reduced f absorption and flat gl cose tolerance curv were demonstra ed.	Tuck & Whittaker (1950)
	1 case	Sprue symptoms first ppeared post partum and reduced f bsorption was demonstrated.	Davi & Brow (1953)
	7 cases	3 out of 7 patients devia ed in the f llowing ways One p tient, earlier treated idiop hic ste torrhoea with folic acid, show ed reduced ylose absorption. 1 patient showed reduced xylose bsorption. 1 patient had pathologic amou of f t in f eces.	Fowler & Cook (1960)
Tw cases of celiac disease		In one case the symptoms first ppeared post partum, fla jejunal mucosa nd gluten-en eropathy were demonstrated; symptoms existed d ring tw previous pregnancies too. In the other case sprue was diagnosed af er last pregnancy though severe sprue symptoms were found during previous pregnancies.	Benson et al. (1964)
	335 cases	Out of 335 p tients 83 were examined regarding the amount of fa in faeces 18 had more than 6 g of f t per day	Giles & Shuttleworth (1958), Giles & Burton (1960), Giles (1966)
Two cases of ad l celiac disease		Both p tient suffer rel pse d ring preg nancy	Samloff et al. (1964)
One case of celiac disease		Exacerbation in four onsecutiv pregn n-cies.	McCleery (1967)
	58 cases	13 out of 57 p tients, 0.39 of 3.58 confinements, were diagnosed as tropical sprue The sprue was discovered towards the end of pregnancy One case w in erpreted as idiop thic teatorrhoea.	Whitfield (1967)
	24 cases	Out of 4 p tients, 10 were from Caribbe n rchipel go, 5 f these later p tients suffered from tropical sprue which was first discovered d ring pregnancy	Law ence & Klips ein (1967)

) Xylose t leran est as used as screening test for malabsorption. Only those p tients w th pathologic xylose test were t rther examined.

Amount f f in ces ged 5.6—.3 g per 24 hours. Biopsy of the small intestine w performed in the case of 7 p tients ed ub-otal and 4 partial illus trophy Folic acid treatment not only affected the anaemia but ca sed plet or p rtial reco ery from sprue as well.

steatorrhoea, however has been described in pregnant women with megaloblastic anaemia of pregnancy compared with women not suffering from megaloblastic anaemia.

During recent years interest in folic acid deficiency during pregnancy has, above all been associated with the possible significance of folic acid deficiency for the development of obstetrical complications in the mother and malformations in the foetus (Hibbard et al 1965). Some authors have argued that pregnant women with folic acid deficiency suffer more frequently from such complications as abortion (Hibbard 1964 Martin et al. 1965 and others) abruptio placentae (Hibbard & Hibbard 1963 Hibbard 1964) haemorrhages (Hourihane et al. 1960) and premature deliveries (Gatenby & Lillie 1960) To sum up it can be said that no evidence has yet been presented for the existence of a causal connection between folic acid deficinecy and the above-mentioned obstetrical complications or foetus malformations (Husain et al. 1963 Giles 1966 Willoughby 1967 Melander 1968 among others)

Post-gastrectomy malabsorption

Malabsorption after partial gastrectomy is considered a common occurrence (cf Lundh 196) By malabsorption both deteriorated digestion and deteriorated absorption are usually meant. The inability to utilise food because of malabsorption leads to the development of various disturbances—for example steatorrhoea, loss of weight, anaemia, protein deficiency lactose intolerance, osteopenia, osteomalacia and iron mineral and vitamin def ciencies. Reduced nutrient supply often contributes to certain of the above disturbances.

The frequency of each single symptom varies in different material. Steatorrhoea is reported as occurring in 20 — 60 /• of the patients who underwent partial gastrectomy (Gordon Taylor et al. 1929 Wollaeger et al. 1946 Butler et al 1954 among others). Complicated cases of partial gastrectomy with steatorrhoea and other pronounced signs of malabsorption occur to a considerably smaller extent and the frequency is said to be less than 1 / of the gastrectomy patients (Bruusgaard 1946 Butler 1961 and others) The frequency figure for steatorrhoea is higher among those who have undergone gastrectomy according to the Billroth II method with modifications than among those who hade undergone gastrectomy according to Billroth I method with modifications (cf French & Crane 1963). The author will hereafter refer to Billroth II and I with minor modifications as BII and BI respectively

Of those patients who have undergone gastrectomy according to BII, 10 — 80 °/• are unable to reach pre-operative or optimal weight. 5 — 24 °/ of those operated on according to BI are similarly unable to increase in weight (cf French & Crane 1963) The composition of the material, and its method of presentation, are largely responsible for the variations in frequency

Anaemia is one of the most common complications of partial gastrectomy After summarising 330 published examinations of about 7,500 patients who had undergone partial gastrectomy Deller and Witts (1962) calculated the frequency of anaemia among gastrectomy patients as 28 / In most cases the anaemia was determined by iron deficiency which occurs even without anaemia in many people who have undergone gastrectomy Iron deposits in patients who underwent gastrectomy according to BII were, measured as non-haemin iron in the bone marrow lower than in healthy people (Weinfeldt 1965)

Uncomplicated megaloblastic anaemia in persons who have undergone partial gastrectomy is considered rather rare, and is reported as occurring in a frequency equivalent to 0.33 — 6 °/• (Ivy et al. 1950 MacLean 1957 Deller & Witts 1962 Hines et al. 1967 and others) In most cases these megaloblastic anaemia are said to be determined by vitamin B_{12} deficiency and only a few by folic deficiency It is stated that relatively often

T bl 5 Works on partially gastrectomized patients ith indings by small bowel biopsy

No. of patients with small bowel changes	Age Sex	Type of gastrectomy	Rem k	La oratory results	Small in estinal m cosa biopsy specimen	A thor
5 out of 61			Prospect e examination with reference point ppe rance of small intestinal mucosa at t me of gastrectomy	2 out of 5 de eloped steatorrhoea	2 patients, who la er de loped st t rrhoe showed i tially grossly abnormal small testinal mucosa	P lley et L 1957
8 ou of 31			Selected cases	2 out of 5 showed steator hoe and abnormal small estinal mucosa	Hyperaemia, oedema a d cl bbing ll	Baird & Dodge 1956
						Forshaw 1958
	47 w	BII	Therapeutic response t gluten-free diet	Det riorated fat absorption. Hypoproteinemia.		
3 ou of 4		BII		1 out of 4 showed decreased yloseabsorption, 4 out of 4 had steator hoea	Atrophic je nitis resembled those seen in idiopathic malabsorption	Joske & Blackwell 1959
2 out of 11	65 m. m.	BII BI	Selected cases	Shilling test with IF pathologic fl t glycose tol rance curve	Subtotal illous atrophy P rt al llous trophy	Shiner & Doniach 1960
16 out of 29			Unselected cases		16 had inflammatory cell infiltration in 5 hape of villi was abnormal nd 4 showed haemorrhage nd oedema	Jones et al. 196.
2 out of 17					"Villous trophy	Ashworth & Chears 1962
12 out of 30		BII	9 out of 10 patients with weigh loss and diarrhoea d mucosal bnormal'ties in small bowel gainst 1 out of 10 essentially wi hout post-operati e compl i ts		12 howed bronic jejun tis out of whom 3 showed villous atrophy without pronounced inflammatory rea tions.	Hradsky & Herout 1963
2 out of 22			Selected cases	1 had p thologic carotin absorption test	Grossly bnormal jejun l biopsies	H mburger et al. 1963
18 out of 24		BII	Selected cases	4 out of 13 had steatorrhoea, 13 out of 19 had decreased xylose absorption	Lea es and ridges i 70 among patients ga t 33 mong controls. One p tient showed p rtial and another btotal illous trophy	Scott et al. 1964
6 out of 31			Unselected cases		P tchy distr'buted mucosal ha ges as those seen i sprue (con ol ted pattern)	Leuthold et al. 1964
			Selected cases		V ryi g from severe ha ges, sim lar o those seen in patient with coeliac disease t normality	Madanagopalan et al. 1965

			Selected cases		Flat mucosa	Hindle & Creamer 1965
5 out of 16			Selected cases		Leaves, 1 pat. with total gastrectomy had flat mucosa[4]	Fry & McMinn 1966
16 out of 42		BII	From 202 unselected cases		Histological evidence of jejunitis and occasional cases showed vill us trophy	Henning et al. 1966
40 examined		BII	Selected cases	20 o t of 40 had steatorrhoea, 3 out of 30 showed pathologic absorption of xylose	6 o t of 40 had minor abnormal ties	Cordni et al. 1966
28 examined		BII	Selected cases (24 operated on for peptic ulcer 3 for cancer and 1 for sarcoma)	8 out of 20 with leaves had decreased xylose bsorption and 6 had pathologic carotin loading test[1]	Out of 24, 18 and 2 showed leaf lik and convoluted villi, respectively[4]	Burhol & Myren 1966
4 examined	45 m.	BII	Selected cases (4 out of 4 patients had an excellent response to gluten-free diet)	Pathologic xylose absorption stea orrhoea	Flat mucosa	Hedberg et al. 1966
	37 m.	GE[5]		Pathologic ylose absorption steatorrhoea	Flat mucosa	
	46 w	BII		Pathologic ylose absorption steatorrhoea		
	48 w	GE[6]		Pathologic ylose absorption steatorrhoea	Flat mucosa	
	50 w	BII	Re-operated on c cording to BI and vagotomy (Therapeutic response to gluten free diet)	P thologic ylose absorption steatorrhoea	Flat mucosa	Rose et al. 1966
	50 w			Normal xylose absorption steatorrhoea	Flat mucosa	Fahrländer & Seigel 1966
76 examined			Selected cases		24 out f 55 showed con ol tions, ridges or leaves. 1 out of 55 had flat mucosa	Roy-Choudri et al. 1966
11 out of 25			Selected cases		Partial or subtotal villous trophy	Nik loff & Kalatcheva 1968
2 examined	52 w 49 w	GE BII	Selected cases (Response to gluten-free diet)	P thologic xylose bsorption P thologic xylose absorption	Partial illous trophy S btotal illous trophy	Weir 1968

1) 6 out f 20 examined patients had metabolic bone disease. Ou of 8 patients with diminished ylose absorption, 5 had metabolic bon disease.
2) 4 showed ed ction of the mucosal activity of succin dehydrogenase.
3) Impaired absorption of D-xylose d vitamin A mainly bserved in patients with jejunal mucosal abnormalities.
4) A third of these patients howed eduction of th mucosal activity f succinic dehydrogenase.
5) Gaster-enterostomy and gotomy
6) Gaste -enterostomy and en eroanastomos.
7) Pathologically low serum folates and pathologically low PGA (pteroyl glutamic acid) absorption.
8) Gaster-en erostomy
9) Re-operated on according to BI.

subnormal serum concentrations of vitamin B_{12} and folates are found in persons who have undergone gastrectomy without there necessarily existing a megaloblastic anaemia at the same time. Subnormal concentrations of vitamin B_{12} in serum among persons who have undergone partial gastrectomy are reported as occurring in 14 — 70 % (Deller & Witts 1962, Hines 1967 and others) and subnormal serum folates among such persons are reported as occurring in 12 — 47 % (Deller & Witts 1962, Gough et al. 1965 and others). The great variations in these frequency figures is probably due, among other things, to differences in test method, the composition of the material and diagnostic criteria.

Hypo-proteinaemia after gastrectomy is considered to be relatively rare (cf. French & Crane 1963). Both and colleagues (1964) found, however, among some hundred patients who had undergone partial gastrectomy about 10 % with subnormal values of serum protein and about 9 % with subnormal values of serum albumen. Henning et al. (1966) found in 1.6 persons who underwent partial gastrectomy statistically significant changes in serum protein including decreased total protein and decreased serum albumen as well as moderately increased gammaglobulin fraction, compared with 99 healthy control persons. Henning et al. (1961) has described pronounced protein deficiency after gastrectomy under the name agastric dystrophy, which is characterised by among other things severe nutrition disturbances with atrophy of musculature, skin fat, skin, hair and nails. In these cases the skin sometimes resembles that which can be found in scleroderma cases.

In recent years special attention has been paid to calcium disturbances and osteopenia after partial gastrectomy. Osteomalacia after gastrectomy has, however, been discussed by Ask Upmark (1939) and described by Vogt (1941), Nicolaysen & Ragard (1955), Pyrah & Smith (1956) and Baird & Oleesky (1957) among others. According to Deller and colleagues (1964) skeleton changes of osteopenia, without elements of ostromalacia, are present in up to 50 % of the patients who have undergone partial gastrectomy. It should be noticed that there was no control material. Morgan and colleagues (1965) found in a check-up of 1?78 persons who had earlier undergone gastrectomy on the indication of gastric or duodenal ulcers, that about 3 % of the women in the material and less than 1 % of the men had osteomalacia. Morgan and colleagues requirements for diagnosis were that serum calcium had been correlated to the amont of serum albumen, that other reasons than osteomalacia for increased alkaline fosfatases in serum had been eliminated and that a therapeutic response to vitamin D therapy was obtained. Biochemical changes in serum reflecting a possibly changed calcium balance have been observed in persons who have undergone gastrectomy concerning, among other things, serum calcium which is subnormal in 6 — 10 % (Deller et al. 1964, Morgan et al. 1965 and others), alkaline fosfatases activity in serum which is increased in 14 — 25 % (Deller et al. 1964, Higgins & Pridi 1966) and serum concentration of vitamin D which can be reduced (Thompson et al. 1966). Osteomalacia has been found by some authors to be associated with the existence of steatorrhoea (among others Baird & Oleesky 1957). Other authors do not believe that a significant connection between malabsorption of fat and the above-mentioned *bone changes exists (Harvald et al. 1962 and* others).

In a large number of works different mechanisms for maldigestion after partial gastrectomy have been discussed. A summarised account of some of the reasons given in literature for such maldigestion is presented below (cf. Lundh 1958, Stammers & Williams 1963). 1) Loss of pyloric function (Friesen & Rieger 1960). 2) Defective stimulation of the pancreas secretion and gall bladder emptying (Borgström et al. 1957, White et al. 1960, Butler et al. 1961). 3) Pancreatico-cibal asynchrony with poor blending of food, pancreas enzymes and bile (Brain & Stammers 1951, Lundh 1958, Butler 1961). 4) Rapid passage

through the small intestine (Glazebrook & Welbourn 1952 Lundh 1958 Illingworth 1960) 5) Bacterial contamination with, among other things blind loop mechanism (Duncan et al 1954 Kinsella et al. 1960 Hess Thaysen 1963) and biliary salt deconjugation (Donaldson 1965) Liver damage (Dittrich et al 1961)

Malabsorption after partial gastrectomy in pronounced cases with steatorrhoea and characteristic symptoms and findings of multiple deficiency can correspond with that observed in other malabsorption diseases such as idiopathic sprue and celiac disease. Some authors have wondered whether in such cases it has not been a question of patients with idiopathic sprue who developed their sprue symptoms after gastrectomy (Paulley et al. 1957 Forshaw 1958 Joske & Blackwell 1959 Scott et al. 1964 Hedberg et al. 1966 and others) Table 5 gives an account of the works on partially-gastrectomised patients with abnormal findings at small bowel biopsy

Histological deviations of varying degrees of severity and even changed enzyme histochemistry in malabsorption after gastrectomy have been described. Findings of subtotal or partial villus atrophy have been quoted as support for the diagnosis celiac disease. In some cases gluten enteropathy and findings of so-called flat mucosa have been considered to verify the diagnosis celiac sprue. Others have maintained that small intestinal mucosa after gastrectomy are not infrequent, and usually determined by jejunitic lesions secondary to the changed physiological conditions which have been caused by gastrectomy (Hradsky et al 1963 Leuthold et al. 1964).

The correlation between the degree of severity of the small intestine changes and the results of biochemical examinations and clinical course have in most cases been remarkably poor This is also the situation with regard to celiac disease (Thurlbeck et al 1960 Rubin et al 1960 a Benson et al. 1964 Samloff et al 1964 and others)

Malabsorption after partial gastrectomy has also been considered to arise through a reduction in the absorbing surface of the small intestine, especially after shunt operations of type BII (cf Stammers & Williams 1963), or through failed post-operative adaptation (Nikoloff et al 1968) Many patients who have undergone partial gastrectomy can normally achieve in time an improved fat absorption (Brain & Stammers 1951 Polak & Pontes 1956 Lawrence et al. 1960).

Malabsorption after partial gastrectomy can sometimes develope insidiously and with relatively few symptoms. It exists for a long time in an unapparent form wh ch perhaps can only be verified with the help of laboratory tests or biopsy examinations.

Deficient digestion and def cient absorption together with insufficient nutrition can sometimes interact in a way that does not allow definite judgement of the significance of each individual defect. Malnutrition after partial gastrectomy would seem to be most often a result of the functional often severe, post cibal complaints which according to the supposed mechanisms of origin have been described under such names as little stomach syndrome, dumping syndrome, afferent loop syndrome and others. Quickly felt repletion and fear of provoking the complaint through food consumption seem to be the most common reasons for the patients to eat less than he needs and thereby to develop malnutrition

III METHODS

D xylose tolerance test

Xylose determination was carried out according to the Roe & Rice method (1948) modified by the author The examination was made in the following way After fasting for 8—10 hours the patient drank 25 g D-xylose dissolved in 500 ml water Urine and blood samples were collected during a further five-hours period of fasting Protein precipitation of urine and blood samples was made according to the Somogyi method, modified. Samples of urine serum reagents, and xylose standards were mixed with an acetic acid acidified rea gent of para bromaniline (Eastman Kodak) saturated with thiourea (Merck) and then heated to 70°C for 10 minutes. After rapid chilling and storing in a dark place for 70 minutes, the extinction was read off in a photometer (Beckman B 10 mm cuvette) at a wavelength of 540 mμ Standards of xylose was prepared from stock solution, and the reagent was usually prepared ex tempore. All samples were examined on the day they were obtained, or in certain cases 1—2 days later In all cases the samples were protein precipitated on the examination day and stored as needed in a dark place at refrigerator temperature Thymol crystals were added to all urine samples.

It was possible to recover the addition of known quantities of xylose to urine and blood in 97—105 % of the added amount.

Double determination of 50 samples of venous blood with a xylose concentration of between 21 and 67 mg% gave a method error of ± 2.4 mg%

Double determination of 50 samples of urine with a concentration of between 7 and 23 mg ± gave a method error of 3.3 mg%.

Xylose tolerance test were carried out on patients admitted to Umeå Hospital in most cases to the rheumatic clinic for treatment of such diseases as spondylosis, arthrosis or lumbago These patients were judged to be free from disturbances which could possibly affect the xylose metabolism The examination material consisted of 31 men and 29 women. The mean average value for xylose excretion in urine during a five-hour period was 7 6 with a standard deviation of ± 1.2 g The mean average value obtained agrees well with earlier findings (Turner 1950 O'Brien et al. 1957 Gardener & Perez Santiago 1956 Benson et al 1957 Vartio 1962 Hess Thaysen and Müllertz 1962).

Determination of fat in faeces

The amount of fat in faeces was determined according to the method of van de Kamer and collegues (1949) The patient collected all faeces during a 3—5 day period, and was encouraged to eat his usual food with the possible adjustment of fat quantities to about 100—125 g per 24 hours. The patient kept a record of the frequency of bowel evacuation etc If bowel evacuation frequency was ir regular the patient was instructed to collect the faeces over a sufficiently long period for at least four bowel evacuation days to have occurred The collection was made in special disposable bowls made of cardboard. In use, the bowl was placed floating on the water in the lavatory bowl After use, the collection bowl was placed in a storage bucket so adapted that the collection bowls remained in the order of collection after they were used. The storage bucket was equipped with a tightly fitting lid. On arrival at the labora tory the samples were frozen and stored at freeze-box temperature (−15 to −20 C) for 1—45 days, after which fat analysis could take place On examination the faeces sample was thawed in a ventilated cabinet, weighed and homogenised after the addition of water Homogenisation was effected with the use of a high frequency homogenisator (Polythron)

which could be put directly into the storage bowl 5—10 g of the homogenised sample was analysed for the presence of fat mea sured as fatty acid according to the above method

Double determination of 50 samples corresponding to a total fat quantity of 1.2—8 g of fat gave a method error of 0.21 g.

The amount of fat in faeces was determined in ten controls, five men and five women, from among those controls mentioned previously in "xylose tolerance test" The mean average value for the amount of fat in faeces per 24 hours was 3.20 g, a standard deviation of 1.29 g These values seem to agree well with the normal values given earlier (cf Cooke & French 1958)

Microbiological folic acid assay of serum. Determination of folic acid was carried out according to Hansen's method (1964) with Lactobacillus casei. The analyses were made at the clinico-chemical central laboratory of Sahlgrenska Sjukhuset in Göteborg

The normal values for serum folates are according to Hansen (1964) higher than 2 9 ng per ml. In May 1969 laboratory gave as the then existing normal values 2.5—15 ng per ml.

Microbiological vitamin B_{12} assay of serum. Determination of vitamin B_{12} in serum was carried out according to Hutner and collegues method (1956) with Euglena gracilis. The determinations were carried out at the clinico-chemical central laboratory of Sahlgrenska Sjukhuset in Göteborg

The normal values, according to information from the laboratory in May 1969 were 810—1000 pg ger ml.

Other investigations

The investigations of both relative and patient material as well as control material were carried out at the medical clinic of Umeå Hospital. This is true of all cases except twenty relatives of sprue patient H, who were investigated by the author at the Cottage Hospital in Överkalix.

Apart from the above-stated laboratory examinations, routine examinations of blood and urine were carried out as well as a number of other examinations which were analysed at the clinico-chemical central la boratory of Umeå Hospital These included inter alia determination of creatine in plasma and urine protein fractions in serum, bilirubin in serum alkaline phosphates in serum, electrolytes in serum among other things.

Details of history for example questioning about possible sprue symptoms and about diet were obtained by the author personally who also made all physical examinations.

Occasionally biopsy of the small intestine was performed, usually at the time of a later examination. Material from the jejunal mucosa was obtained with the help of a Multi Purpose Suction Biopsy Tube (Quinton Instrument Co Seattle) The tube position was checked by means of X-ray

The biopsy specimen was attached to a piece of filter paper and fixed in 2% glutaraldehyde. During fixation the mucosa was inspec ted and in some cases photographed trough a dissection microscope. The preparation for histological examination was bedded in paraffin (paraplast) If several biopsy frag ments were obtained, disacharidase activity was usually determined in homogenisate of the mucosa according to Dahlqvist's method (1963)

Statistical methods

Means, standard deviations, standard errors in double tests and measures of skewness were calculated according to current methods in statistical textbooks (Peatman 1963)

Differences between two means were ana lysed with the help of Student's t-test.

Differences between proportions were in most cases analysed with the help of Fischer's exact probability test and occasionally through Chi-square analysis or by expansion of bi nomials.

Most numerical calculations were carried out with the help of an electronic desk computer Olivetti Programma 101

IV MATERIAL

In this work idiopathic non tropical sprue means a disease of unknown etiology characterised by long-drawn-out often intermittent course with symptoms relating to disturbed function of the small intestine which manifests itself in particular through generally diminished absorption of fat and fat-soluble vitamins, carbohydrates, proteins or their digests and folic acid. The symptom picture is usually characterised by disturbances of the intestinal function such as meteorism excretory disorders usually with frequent, massive and fatty excretion, and deficiency symptoms such as loss of weight, folic acid deficiency anaemia, osteopenia, protein and multiple vitamin deficiency disorders. Characteristic of the disease is that a therapeutic response to an elimination diet, especially gluten free food, is often obtained, and that histological changes in small intestinal mucosa are usually found, which for the most part in untreated cases are typical. As previously mentioned the disease is very close to coeliac disease of childhood Little is known about its relation to tropical sprue.

There is no single symptom, physical sign or laboratory test with which the diagnosis idiopathic sprue can be definitely established. The diagnonsis must be based on probable grounds, partly through identification with the empirically known characteristics of the disease and partly through the exclusion of other causes of malabsorption. The following criteria for the diagnosis idiopathic non tropical sprue have been used in this study

1 anamnestic information and physical signs in agreement with the diagnosis.
2. steatorrhoea, diminished xylose or glycose absorption and decreased blood folates during some phase of the disease.
3 several signs of generally disturbed function of the small intestine such as loss of weight, decreased blood lipids, deficiency in fat soluble vitamins, deficiency pattern in X ray examination of small intestine etc.
4 exclusion of other diseases which can give similar symptoms and examination findings.
5 the existence of histological changes in the small intestine
6 therapeutic response to elimination diet, especially gluten free.
7 signs of celiac disease during childhood.

The examination material consisted of

A Patients treated at Umeå Hospital s medical clinic during the period 195_—1965 under the diagnosis idiopathic non-tropical sprue.
B. Relatives of those sprue patients treated at Umeå Hospital s medical clinic during the period 195?—1965 and matched control material

C. Data on idiopathic non-tropical sprue, megaloblastic anaemia of pregnancy and partial gastrectomy obtained from hospital s annual reports to the Social Welfare Board and operation reports in the surgical clinics of Västerbotten, and Swedish Official Statistics.

D Information obtained from hospital records about patients with idiopathic sprue and earlier diagnosed megaloblastic anaemia of pregnancy

E. Women who during the period 1931—1965 were treated under the diagnons megaloblastic anaemia of pregnancy at hospitals in the county of Västerbotten and matched control material.

A. Patients treated at Umeå Hospital's medical clinic during the period 1952—1965 under the diagnosis idiopathic non-tropical sprue

The author s material of manifest idiopathic sprue consists of twenty consecutive cases treated at the medical clinic during the said

period. Table 6 gives clinical details and examination results for these twenty patients. Ten of the patients were women, two of whom had earlier had megaloblastic anaemia of pregnancy Nine of the twenty patients had earlier undergone partial gastrectomy in eight cases because of peptic ulcer disease and in one case because of a gastric polypus.

By the beginning of 1969 nine patients had died, and autopsies were performed on 7 of the deceased. In all cases the result of the autopsy gave further support for the diagnosis idiopathic sprue. Concerning sprue patients who had undergone partial gastrectomy gluten free food was judged effective in 3 cases and in 2 cases the effect was uncertain. For those who had not undergone partial gastrectomy a dramatically good effect was obtained in 2 cases and some effect in 4 cases.

B *Relatives of those sprue patients treated at Umeå Hospital's medical clinic during the period 1952—1965 under the diagnosis idiopathic sprue and matched control material*

The relative material was traced with the help of information obtained from parish registers and census records. These relatives, consisting of parents, children, grandchildren, siblings, nephews and nieces, were invited to take part in an investigation. Most of the people asked agreed to take part in the investigation, which comprised among other things history taking, physical examination and laboratory examinations including xylose tolerance test, determination of fat in faeces and microbiological folic acid assay of serum. The examinations were carried out at the medical clinic of Umeå Hospital. 24 persons, relatives of sprue patients H who had undergone partial gastrectomy (Table 6), were examined by the author at the cottage hospital in Överkalix. Only persons aged fifteen or over were examined.

A control material corresponding to the relative material with regard to age and sex was examined in close connection with the examination of the relatives. The control material was selected at random from the population register An exception to this concerned those relatives in Överkalix, who were examined without comparison with matched controls.

The material of the above-mentioned sprue patients relatives comprises 56 men and 38 women, of whom 15 men and 10 women are relatives of the sprue patients who had not undergone partial gastrectomy and 41 men and 28 women are relatives of those who had undergone partial gastrectomy The former group (non-gastrectomy) includes three men and one woman related to the sprue patients who had had megaloblastic anaemia of pregnancy The family relationships can be seen in Fig 1 which gives the genealogical table of each sprue patient.

Sprue patient P III 1 (Fig 1) who had undergone partial gastrectomy is the older sister of sprue patient F who had not undergone partial gastrectomy The parents of these patients proved to be cousins. There are also detailes of intermarrige concerning family I (Fig. 1) where a niece (I III.3) of proband I II.5 with idiopathic sprue after partial gastrectomy is married to the son of one of the proband s double cousins and in family H a niece (H III.2) of sprue patient H.II 8 with idiopathic sprue after partial gastrectomy (Fig 1) is married to a "double" cousin on the mother s side Because of their age, none of the children of these marriages between people by marriage were qualified for examination by the author There was a possibility that the father of sprue patient E II:1 might be a distant relative of his wife, the patient s mother but this could neither be confirmed nor dismissed.

C. *Data on idiopathic non tropical sprue megaloblastic anaemia of pregnancy and partial gastrectomy obtained from hospital's annual reports to the Social Welfare Board and operation report in the surgical clinics of the county of Västerbotten and Swedish Official Statistics*

The statistical material for calculating the frequency of idiopathic sprue, megaloblastic

T ble 6. Data and examination results on twenty patients diagnosed as idiopathi non-tropical sprue t medical clinic of Umeå hospital during the period 1952 1965

Family and sex	Age, when diagnosed	Number of pregnancies	Weight loss (kg)	Erythropoesis	Free HCl	Serum protein (g%)	Serum B (pg/ml)	Schilling Test I	Schilling Test II	Faecal fat % of dry weight	Faecal fat g per 24 h.	Xylose tolerance test (g per 5 h urin)	Glycos tolerance test (increase in mg%)	Serum folates (ng/ml)	Small bowel biopsy (dissect g microscopy)	Partial gastrectomy Method Years Indicatio	Age of death
A, w	54 yrs (1959)	5	+	M		low	210	1 1	3.0	59			22				56
C, w	33 yrs (1960)	2	>10	m						68			5				46
F m	46 yrs (1960)		3	M	pro ed		175	1.1	2.1		39	3.0		1 9			
G w	54 yrs (1960)	t	15	m		low	155	1 5	<1	30	40	0.8	20	1 1			56
K, w	50 yrs (1963)		8			low		2.5	1 4	40		1.8	40	2.4			52
N m	60 yrs (1964)		9	N			230			56		1 1		1.5	flat		63
R, m	54 yrs (1965)		5	M	proved	low	285	16			32	2 1	20	0.4	flat		
S, m	32 yrs (1965)		5								32	2.4			(fla)f		
U m	63 yrs (1965)		5	m	proved			17		56		1.5		1 8	flat		
Patients with earlier anaemia of pregnancy																	
M, w	56 yrs (1964)	2a	8	M	proved	low	145				11	0.1	6	0.7	ridges		
O w	32 yrs (1964)	3a	3	M	proved	low	245	40			16	1 1	21	0.4			
Patients with earlier partial gastrectomy																	
B, m	40 yrs (1959)		12	N		low	265	8 3	9 6	83		2.8				BII 1952 ulc. duod.	
			2			low		12		50		6 8			con ol ted[d]	BI 1962	
D m	63 yrs (1960)		11	m		low	225			58		3.9				BII 1956 lc. ventr	70
E, m	52 yrs (1960)		8			low		5.7		32		3				BII 1955 lc. ventr	
			5				200			46		3 9				BI 1961	
H, w	55 yrs (1962)	5	12				77	1.6	23	51	22	2.5		3.2	ridges	BII 1958 pol p. en	56

L, w	67 yrs (1963)	1	10	M	low	96	8	21	68		3.5		0 7	con ol ed	BII 1952 ulc. duod.	
L, m	55 yrs (1963)		8	N		170	6 7	9...		87	3.3		2.2		BII 1943 lc. duod.	
P w	61 yrs (1964)	3	7	m		230				9	3.0		2.0	fla	BI 1961 ulc. ventr	
Q w	71 yrs (1963)		5	M	low	225				9.6	3.5		<3.0		BII 1962 lc. vent	74
T m	50 yrs (1965)		15		low	88			+++					flat	BII 1950 ulc. entr	40
Normal values				N	pro ed >5.5	>150	>8	>10	<25	<6	>4.2	>40	>2.9			

Comments N = normoblastic M = megaloblastic; m = intermediat f rms f megaloblasts nd/or macroblastic myelopoes.

) sprue symptoms first appeared during the first pregnancy
) report from nother hospital on histological examination of biopsy specimen ndicated subtotal villous trophy
) exacerbation during first pregnancy when megaloblastic aemia was diagnosed.
) biopsy performed during remission on gl ten-free diet.
) sprue symptoms first appeared dur g he third pregnancy
) biopsy performed d ring remission on trea ment with cort costeroids.

Case-record o. of probands A—U 2477 315 282, 1761 933 2741 2410, 2401 271 683 986, 90, 180, 244 2123 928, 68, 1944 2460 and 400(N) resp.

anaemia of pregnancy and partial gastrectomy in the county of Västerbotten and in Sweden was collected. The author studied the files of the Social Welfare Board and annual reports from hospitals concerning said diagnosed or surgically treated diseases for the period 1952—1963 This investigations was supplemented by a study of the case-records of adult patients who according to the above annual reports had been treated in hospitals under the diagnosis idiopathic sprue, coeliac disease or some other synonymous term. By means of these two studies material was obtained for estimating the frequency in Sweden of diagnosed idiopathic sprue and the frequency of partial gastrectomy performed because of peptic ulcer disease. A study of selected parts of the case-record files in Skellefteå, Umeå and Lycksele hospitals provided material for calculating the frequency in Västerbotten of diagnosed idiopathic sprue and partial gastrectomy performed because of a gastric or duodenal ulcer Forthermore, from this study of records details were obtained of patients treated in Västerbotten hospitals under the diagnosis megaloblastic anaemia of pregnancy

From the Central Bureau of Statistics was obtained both archival material and unpublished material about the population and its shifts in Sweden and Vasterbotten. This information was used for calculating the above-mentioned frequencies of idiopathic sprue, partial gastrectomy and megaloblastic anaemia of pregnancy

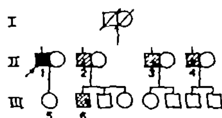
D *Information obtained from hospitals records about patients with idiopathic sprue and earlier diagnosed megaloblastic anaemia in pregnancy*

Two of the ten women included in the author's primary idiopathic sprue material had had megaloblastic anaemia of pregnancy A special study was made of the other women in the primary material with regard to the possible occurrence of megaloblastic anaemia of pregnancy No definite information, however could be discovered about earlier megalo-

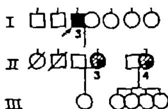
Γ 1 Genealogical tables of patients w th diagnosed idiopathic sprue.

Families with probands who had been subjected to partial gastrectomy

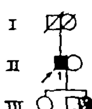
Family B



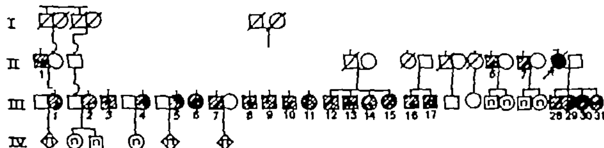
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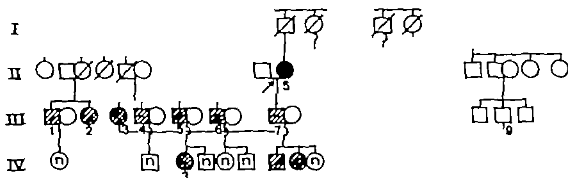
Family E



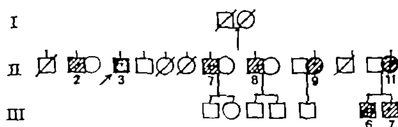
Family H



Family I



Family L



Family P (=F)

I

II

III 1 2 4 6

IV 1 4 5 6 7 n

V 1 2 3

Family Q

I 1 4 8

II 2 6

III 4 5

IV

Family T

I 1

II 1 2 4 5

III

Families with probands not being subjected to partial gastrectomy

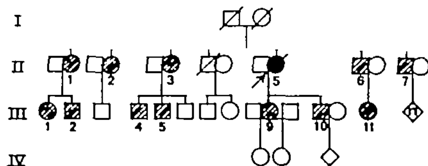
Family A

I 4 5 6

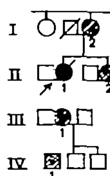
II n n n n n n

Family C

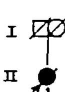
Family F
(= Family P)



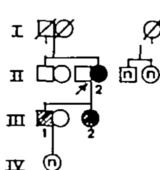
Family G



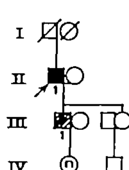
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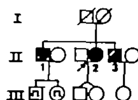
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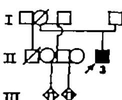
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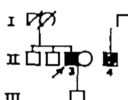
Family O



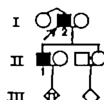
Family R



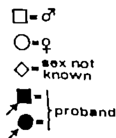
Family S

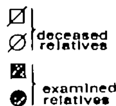


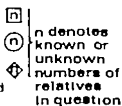
Family U



Signet







A–S denotes family

I–V " generation

1–31 ' number of individes in the generation

blastic anaemia in connection with pregnancy or otherwise. The results of these investigations are presented in Table 6 from which it can be seen among other things that the sprue disease in patient C first appeared in connection with her first pregnancy and symptoms occurred in her second pregnancy also

In the previously mentioned study of case-records of patients treated in hospitals under the diagnosis idiopathic sprue coeliakie and so on, the author found ten more women with diagnosed idiopathic sprue who in connection with pregnancy had had megaloblastic anaemia. Of these women seven definitely and three probably had had megaloblastic anaemia of pregnancy or puerperium.

E. Women who during the period 1931—1965 were treated under the diagnosis megaloblastic anaemia of pregnancy at hospitals in the county of Vasterbotten and matched control material

As previously stated, selected parts of case-record files in Skellefteå, Umeå and Lycksele hospitals were stud ed with regard to inter alia patients treated under the diagnosis megaloblastic anaemia of pregnancy During the period 1932—1965 a total of 57 women were treated at hospitals in the county of Västerbotten under the diagnosis megaloblastic anaemia of pregnancy and registered under different codes two of these women appear in the above-mentioned primary material (Table 6) Up to Januari 1968 seven women had died. The death certificates have been studied and do not occasion any comment.

36 of the remaining women with earlier megaloblastic anaemia of pregnancy accepted the offer of a check-up (Table 17) Althogether twelve women could not find the time to participate in the check-up

36 out of 55 women who had had megaloblastic anaemia of pregnancy 8—37 an average of 17.7 years earlier were during 1968 examined by the author A control material chosen with regard to age and sex, selected at random with the help of information from the population register was examined in connection with the examination of the above mentioned patients with earlier megaloblastic anaemia of pregnancy (Table 17)

V RESULTS

1) *Examination of relatives of the sprue patients treated at Umeå Hospital's medical clinic during the period 1952—1965 and of randomly-selected controls matched to these relatives*

Biochemical examinations with the aim of demonstrating possible signs of general malabsorption were carried out by means of D-xylose tolerance test, determination of faecal fat and microbiological folic acid assay of serum. 94 relatives of sprue patients treated at the medical clinic of Umeå Hospital during the period 1952—1965 and 74 controls matched to these relatives were examined in the above way

D-xylose tolerance test on sprue patient s relatives and their controls

The result of D-xylose tolerance test on 93 relatives of sprue patients and 72 of their matched controls is shown in Tables 7 and 8

From Table 8 it can be seen that the mean average value for xylose excretion in the urine during a five-hour period after peroral administration of 25 g D-xylose is significantly

Table 7 Results of D-xylose tolerance test carried out on 93 relatives of sprue patients and 72 matched controls.

Relatives Designation according to genealogical table		Age	Relationship	Amount of xylose in urine per 5 h	Deviation points	Controls: Signum	Amount of xylose in urine per 5 h	Deviation points
Relatives of sprue patients who had not undergone partial gastrectomy								
A II	6	58	brother	9.1	42	EF	—	(50)
	4	65	sister	6.4	60	MN	5.0	69
C III	10	25	son	4.1	75	KA	10.5	33
	9	27	daughter	3.6	78	EL	6.9	57
II	3	55	sister	4.2	74	EJ	6.5	59
	2	59	sister	5.7	64	AM	5.4	66
	6	48	brother	6.5	59	GJ	5.9	63
	1	56	sister	4.0	75	KK	8.1	49
	7	43	brother	5.5	66	IN	7.5	5
III	11	17	niece	5.9	63	GO	7.6	52
	1	4	niece	6.7	58	UBH	6	61
	2	22	nephew	10.8	31	BE	9.7	38
	4	33	nephew	6.1	6[illegible]	RV	7.1	55
	5	26	nephew	6.9	57	SB	9.7	38
F (see I)								
G I	2	83	mother	6.0	62	TS	5.1	68
III	1	35	daughter	8.3	47	AB	7.5	52
IV	1	17	grandson	5.4	66	LGG	9.5	39
II	2	55	sister	—	(50)	IK	7.9	50
M III	1	26	son	4.0	76	KF	9.0	43
	2	16	daughter	7.[illegible]	54	HA	7.1	55
N III	1	30	son	11.2	28			
O II	1	35	brother	5.1	68	AB	6.8	57
	3	28	brother	9.7	38	FB	8.2	48
S II	4	46	half-brother	3.6	78	EB	8.9	43
U II	1	33	son	6.0	62	OS	6.8	57
Relatives of sprue patients who earlier had undergone partial gastrectomy								
B II	2	49	brother	8.8	44	AS	9.4	40
	3	43	brother	9.9	37	KL	9.8	37
	4	39	brother	6.1	62	TL	6.[illegible]	58
III	6	17	nephew	7.7	51	AL	8.5	46
D II	3	32	daughter	7.0	56	BK	9.0	43
	4	30	daughter	5.4	66	BR	10.6	32
E III	2	25	daughter	8.5	46	LL	9.7	38
H III	28	32	son	8.3	47	AN	8.2	48
	29	25	daughter	6.2	64	SH	6.2	61
	30	23	daughter	7.5	52	LA	9.4	40
	31	18	daughter	8.[illegible]	48	EJ	10.7	31
II	1	72	brother	9.0	43			
	6	61	brother	7.5	52			
	7	59	brother	1.1	95			
III	1	46	niece	8.4	47			
	2	44	niece	9.5	39			
	3	42	nephew	5.2	68			
	4	40	niece	8.7	45			
	5	37	niece	8.2	48			
	7	30	nephew	7.0	56			
	8	29	nephew	5.4	66			
	9	27	nephew	7.6	52			
	6	36	niece	9.5	39			
	10	22	nephew	8.2	48			
	11	19	niece	10.0	36			
	16	43	nephew	7.7	51			
	17	40	nephew	6.6	58			
	12	39	nephew	9.7	38			
	13	41	nephew	5.3	60			
	14	39	niece	6.5	67			
	15	38	niece	7.7	51			

Relatives Designation according to genealogical table		Age	Relationship	Amount of xylose in urine per 5 h	Deviation points	Controls Signum	Amount of xylose in urine per 5 h	Deviation points
I:III	7	44	son	8.5	46	EF	7.0	56
IV	8	19	grandson	9 1	42	GK	10.2	38
	9	18	granddaughter	3.6	78	AL	8.0	49
III	1	47	nephew	3.2	81	BM	10.4	33
	2	41	niece	3 9	76	BA	8.9	43
	5	42	nephew	6.3	60	KL	8.0	49
	4	45	ephew	6.4	60	RE	5.2	68
	6	41	nephew	8 4	47	BW	8.9	43
	3	46	niece	7.0	56	MH	9 9	37
IV	3	16	great-granddaught.	4.3	74	AS	9 4	40
L:II	9	47	sister	6 4	60	AN	10.4	33
	2	59	brother	8.7	45	TJ	7.2	55
	4	55	brother	9.6	39	VB	6.3	60
	8	48	brother	5 4	66	EL	5.3	67
	7	50	brother	6.4	60	GN	8.0	49
	11	41	sister	6.2	61	AMO	8.5	46
III	6	19	nephew	9 1	42	NF	9.3	41
	7	16	nephew	8.8	44	HEH	9.8	37
P:IV	1	42	son	6.2	61	KLS	7 1	55
V	2	1	grandson	5.7	64	EJ	6 8	57
	1	22	grandson	4.3	74	RS	7.6	52
	3	19	grandson	6.4	60	AB	7.5	52
III	6	68	brother	5.2	67	BB	—	(50)
	2	56	brother	9 6	39	BG	6.2	61
	4	51	brother	3.3		BMH	7.7	51
IV	5	23	nephew	9.3	41	JO	9.0	43
	4	27	niece	7 9	50	DL	7 1	55
	6	17	nephew	4.0	76	RL	7.0	56
	7	16	nephew	7.5	52	LGR	7.9	50
Q:I	1	70	brother	3.5	79	JN	7 4	53
	8	53	sister	5.2	68	VB	7.6	52
II.	6	45	niece	6.0	62	MH	6 9	57
	2	30	niece	6.3	60	MR	8.9	43
III	4	23	great-granddaught.	7.2	55	EL	7 4	53
	5	21	great-grandson	9 4	40	SVL	5 4	66
T:I	1	80	father	4 2	74	US	5.5	66
II	2	48	sister	8.7	45	VB	6.7	58
	4	47	sister	7.0	56	AML	8 2	58
	5	40	sister	9.5	39	UH	8.9	43

) The proband had earlier had megaloblastic anaemia of pregnancy

*) Proband F is not included in the summary of relatives deviations.

lower for relatives of the above-mentioned sprue material than the mean average value for the controls ($p < 0.005$).

It can be further seen from Table 8 that there is significantly less excretion in urine after peroral D-xylose tolerance test, indicating a reduced xylose absorption, in relatives C, I M P Q and S compared with the whole material of matched controls.

The outcome of the xylose tolerance test in the controls was analysed with regard to possible differences between sex and age. Comparison with the whole control material is considered justified, since no definite difference between the sexes or correlation between the test results and the patient's age could be demonstrated.

Each value of the amount of xylose per five hours urine has been transformed to deviation points according to the following formula:

$$\text{Deviation points} = 50 - \frac{x - M_c}{SD_c}$$

x = current value of the amount of xylose per five hours urine

M_c = mean average value of the amount of xylose in urine per five hours' urine in controls

SD_c = standard deviation of the amount of xylose in urine per five hours urine in controls

Thus small amounts of xylose in urine as seen in sprue correspond to a large number of deviations points

Out of 34 examined relatives of patients with idiopathic sprue who have not undergone partial gastrectomy 8 have a reduced xylose absorption corresponding to at least 70 deviation points.

The finding of 70 deviation points concerning xylose tolerance test in an examined relative indicates that the relative in question, compared with the controls, lies on or below the mean average value of the amount of urine xylose excretion in the controls minus two standard deviations.

Out of 69 examined relatives of sprue patients who earlier undergone partial gastrectomy 9 have a reduced xylose absorption corresponding to at least 70 deviation points. None of the 72 matched controls have reduced absorption corresponding to 70 deviation points or more. The number of relatives with reduced xylose absorption judged by the xylose test among relatives of both sprue patients who have not undergone partial gastrectomy and those who have differs significantly from the number of persons with reduced xylose absorption among the controls ($p<0.00006$ and $p<0.002$ respectively)

Table 8 Mean average values of xylose absorption in sprue patients' relatives and their controls. Mean differences according to Student's t-test.

Designation of family	Relatives number of	mean of amount xylose in urine per 5 h.	standard deviation	Differences between the means in families concerned and the mean in all control persons: t	d f)	p
A	2	7.7500	1.9091	0.1359	70	
B	4	8 1250	1.6214	−0.2920	74	
C	12	5 8333	1 9360	4.2258	82	<0.0005
D	2	6.2000	1 1313	1.5786	72	<0.10
E	1	8.5				
G	3	6.5666	1.3312	1.5011	73	<0.10
H	24	7 4583	1.9225	1.1534	94	<0.15
I	10	6.0700	2.2040	3.3799	80	<0 0025
L	8	7.5750	1.6289	0.5692	78	
M	2	5.6000	2.2627	2.1119	70	<0.025
N	1	11.2				
O	2	7 4000	3.2526	0.4497	70	
P (=F)	10	6 6100	1 9381	2.4406	80	<0.01
Q	6	6.2666	1 9777	2.4913	76	<0.01
S	1	3.6				<(0.0001)
T	4	7.3500	2.3444			
U	1	6 8				
All relatives				Differences between the mean in all relatives and m he mean in all control persons: t	d.f	p
	94	6 8600	2.0125			
All controls						
	72	7.8972	1.5097	3.6284	164	<0.0005

) d.f = degree of freedom

Table 9 Amount of fat in faeces per 24 hours, determined in 84 relatives of sprue patients and 65 matched controls

Relatives: Designation according to genealogical table		Age	Relationship	Amount of fat (in g) per 24 hours	Deviation points (log fat)	Controls Signum	Amount of fat (in g) per 24 hours	Deviation points (log fat)
Relatives of sprue patients who had not undergone partial gastrectomy								
A I	6	58	brother	3.7	54	EF	3.4	52
	4	65	sister	4.6	59	MN	3.6	53
C III	10	25	son	6.3	66	KA	—	(50)
	9	27	daughter	7.0	68	EL	2.3	43
II	3	55	sister	1.9	39	EJ	3.0	49
	2	59	sister	7.1	69	AM	4.1	56
	6	48	brother	9.5	75	GJ	5.7	64
	1	56	sister	4.8	60	KA	2.6	46
	7	43	brother	2.3	43	IN	3.3	51
III	11	17	niece	1.6	35	GO	—	(50)
	1	24	niece	1.6	35	UBH	1.5	33
	2	22	nephew	6.8	68	BE	2.3	43
	4	33	nephew	—	(50)	RV	5.1	61
	5	26	nephew	4.7	60	SB	4.0	56
F (see P)								
G.I	2	83	mother	10.8	78	TS	5.8	64
III	1	35	daughter	3.9	55	AB	5.3	62
IV	1	17	grandson	2.7	47	LGG	—	(50)
II	2	55	sister	6.6	67	IK	2.1	41
M[1].III	1	26	son	10.8	78	KF	2.0	40
	2	16	daughter	4.0	56	HA	5.1	61
N III	1	30	son	—	(50)			
O[1] II	1	35	brother	8.3	72	AB	3.1	50
	3	28	brother	—	(50)	FB	4.2	57
S.II	4	46	half brother	11.2	79	EB	2.0	40
U.II.	1	33	son	1.9	39	OS	4.5	58
Relatives of sprue patients who earlier had undergone partial gastrectomy								
B.II	2	49	brother	14.7	85	AS	3.2	51
	3	43	brother	4.0	56	KL	2.6	46
	4	39	brother	3.0	49	TL	2.6	53
III	6	17	nephew	4.2	57	AL	3.9	46
D II	3	32	daughter	3.4	52	BK	1.1	26
	4	30	daughter	5.8	64	BR	2.8	48
E.III	2	25	daughter	3.0	49	LL	2.6	46
H III	28	32	son	6.4	65	AN	4.0	56
	29	25	daughter	2.1	41	SH	3.1	50
	30	23	daughter	1.9	39	LA	4.9	60
	31	18	daughter	1.4	32	EJ	2.9	49
II	1	72	brother	2.5	45			
	6	61	brother	5.4	63			
	7	59	brother	4.5	58			
III	1	46	niece	3.9	55			
	2	44	niece	3.5	53			
	3	42	nephew	1.9	39			
	4	40	niece	—	(50)			
	5	37	niece	2.6	46			
	7	30	nephew	3.7	54			
	8	29	nephew	5.9	65			
	9	27	nephew	3.8	55			
	6	34	niece	3.1	50			
	10	21	nephew	5.0	61			
	11	19	niece	—	(50)			
	16	43	nephew	5.9	63			
	17	40	nephew	4.1	56			
	12	39	nephew	—	(50)			
	13	41	nephew	6.0	65			
	14	39	niece	3.9	55			
	15	38	niece	—	(50)			

(Continued on next page)

Relatives Designation according to genealogical tables		Age	Relationship	Amount of fat (in g) per 24 hours	Deviation points (log fat)	Controls Sign m	Amount of fat (in g) per 24 hours	Deviation points (log fat)
I:III	7	44	son	4.3	57	ET	3.0	40
IV	8	19	grandson	—	(50)	GK	—	(50)
	9	18	granddaughter	4.1	56	AL	2.8	48
III	1	47	nephew	7.1	70	BM	3.1	50
	2	41	niece	6.1	65	BA	5.1	61
	5	42	nephew	13.3	83	KL	0.8	19
	4	43	nephew	6.9	68	RE	4.6	59
	6	41	nephew	11.6	80	BW	3.8	55
	3	46	niece	3.6	53	MH	3.9	55
IV:	3	16	great granddaught.	3.0	49	AS	2.4	44
L II:	9	47	sister	2.8	48	AN	1.5	33
	2	59	brother	8.5	73	TJ	4.2	57
	4	55	brother	2.4	44	WB	5.6	64
	8	48	brother	3.4	52	EL	2.2	42
	7	50	brother	4.2	57	GN	2.8	48
	11	41	sister	1.3	30	AMO	—	(50)
III:	6	19	nephew	3.7	54	NF	1.4	32
	7	16	nephew	3.0	61	HEH	3.4	52
P:IV	1	42	son	1.6	35	KLS	—	(50)
V:	2	21	grandson	4.8	60	EJ	4.3	57
	1	22	grandson	9.0	74	RS	3.1	50
	3	19	grandson	4.2	57	AB	—	(50)
III	6	68	brother	1.8	38	BB	1.3	30
	2	56	brother	2.0	40	BG	5.6	63
	4	51	brother	(11.2)		BMH	3.4	52
IV	5	23	nephew	2.0	40	JO	—	(50)
	4	27	niece	—	(50)	DL	1.6	35
	6	17	nephew	7.9	71	RL	4.0	56
	7	16	nephew	1.4	32	LGR	2.1	41
Q:I	1	70	brother	6.2	66	IN	5.4	63
	8	53	sister	5.8	64	VB	5.9	65
II:	6	45	niece	—	(50)	MH	5.8	64
	2	30	niece	1.4	32	MR	3.0	49
III:	4	23	great-granddaught.	1.2	28	EL	2.4	44
	5	21	great-grandson	1.6	35	SuL	1.7	36
)T:I	1	80	father	7.0	68	US	3.6	53
II	2	48	sister	3.7	54	VB	3.9	55
	4	47	sister	1.6	35	AML	3.2	31
	5	40	sister	3.7	54	UH	—	(50)

) The proband had earlier had megaloblastic anaemia of pregnancy
*) Proband F is not included in the summary of relatives deviations.

Determination of fat in faeces carried out on sprue patients relatives and their controls

The results of the determination of faecal fat per 24 hours in 84 sprue patients' relatives and 65 controls are shown in Table 9

The values for the amount of fat in faeces in the controls do not have normal distribution The distribution of the control person s faecal fat is skew with a skewness to the right $\left(\frac{m^3}{(\sqrt{m^2})^3} = 0.68\right)$. On the other hand the logarithms of fat in faeces do not have skew distribution.

From Table 10 it can be seen that the mean average value for the amount of fat in faeces per 24 hours for relatives of the above-mentioned sprue patients is statistically sig-

nificantly higher than the mean average value for the controls ($p < 0.005$). It can be further seen from the Table that there is a significantly higher fat quantity in faeces, indicating poor fat absorption, in case of relatives B, C, G, I, M, O and S compared with the whole control material. The values for the amount of fat in faeces for the controls were analysed with regard to a possible difference between the sexes and a possible correlation between the test result and the person's age. Comparison with the whole control material is considered justified since no difference or correlation could be demonstrated.

Each value of the amount of faecal fat in Table 9 has been converted to deviation points by means of the following formula

$$\text{Deviation points} = 50 + \frac{F - M_0}{SD_c}$$

F = logarithm of the current value of the amount of fat in faeces per 24 hours

M_0 = mean average value of the log amount of fat in faeces per 24 hours in the controls.

SD_c = standard deviation of the log amount of fat in faeces per 24 hours in the controls.

Thus large amounts of faecal fat, as seen in sprue patients, correspond to a large number of deviation points.

Out of 31 examined relatives of sprue patients who had not undergone partial gastrectomy 7 show signs of a reduced fat absorption corresponding to at least 70 deviation points.

Table 10. Mean average values of log fat in faeces in sprue patients' relatives and their controls. Mean differences according to Student's t-test.

Designation of family	Relatives numbers of	mean of log amount fat in faeces per 24 h	Standard deviation	Differences between the means in families concerned and the mean in all control persons: t	d.f	p
A	2	0.6155	0.6070	0.9164	65	
B	4	0.7174	0.3065	2.2278	67	<0.025
C	11	0.6098	0.2903	1.7378	74	<0.05
D	2	0.6474	0.1637	1.1379	65	
E	1	0.4771				
G	4	0.6935	0.2837	2.0079	67	<0.025
H	20	0.5517	0.1915	1.2412	83	
I	9	0.7730	0.2253	4.0856	72	<0.0005
L	8	0.5376	0.2397	0.4315	71	
M	2	0.8197	0.3077	2.3817	65	<0.0125
N	—	—				
O	1	0.9191				(<0.001)
P (=F)	9	0.4848	0.3085	0.0915	72	
Q	5	0.3970	0.3504	0.8235	68	
S	1	1.0492				(<0.001)
T	4	0.5464	0.2626	0.5464	67	
U	1	0.2788				
All relatives	84	0.6079	0.2714	Differences between the means in all relatives and the mean in all control persons: t	d.f	p
All controls	65	0.4915	0.1907	2.8137	147	<0.005

*) d.f = degrees of freedom

Table 11 Results of microbiological folic acid assay of serum in 92 relatives of sprue patients and 68 matched controls

Relatives Designation according to genealogical tables		Age	Relationship	Serum folates	Deviation points (log serum folates)	Controls Signum	Serum folates	Deviation points (log serum folates)
Relatives of sprue patients who had not undergone partial gastrectomy								
A I	6	58	brother	5.3	44	EF	4.1	51
	4	65	sister	8.6	31	MN	4.1	51
C_1II	10	25	son	2.5	65	KA	5.3	44
	9	27	daughter	4.4	49	EL	4.5	49
II	3	55	sister	5.3	44	EJ	5.[illegible]	45
		59	sister	3.5	55	AN	9.1	29
	6	48	brother	1.6	77	GJ	2.4	66
	1	56	sister	5.3	44	KK	2.9	61
	7	43	brother	2.5	65	JN	3.7	54
III	11	17	niece	4.6	48	GD	—	(50)
	1	24	niece	6.1	40	UBH	3.9	53
	2	22	nephew	4.2	50	BE	2.2	68
	4	33	nephew	3.1	59	RV	8.3	32
	5	26	nephew	7.9	33	SB	2.6	64
F (see P)								
G I	2	83	mother	2.7	62	TS	7.9	33
III	1	35	daughter	3.9	52	AB	4.8	47
IV	1	17	grandson	2.7	62	LGG	4.7	47
II	2	55	sister	2.4	66	JK	5.4	4
M III	1	26	son	1.9	72	KF	4.6	48
	2	16	daughter	3.5	55	MA	4.0	52
N_1II	1	30	son	3.4	56			
O^1II	1	35	brother	1.9	72	AB	2.0	71
	3	28	brother	3.2	58	FB	3.6	55
S II	4	46	half brother	2.8	61	EB	6.5	38
U II	1	33	son	2.6	63	OS	2.7	62
Relatives of sprue patients who earlier had undergone partial gastrectomy								
B_1II	2	49	brother	2.0	71	AS	7.8	39
	3	43	brother	—	(50)	KL	2.4	66
	4	39	brother	4.9	46	TL	4.9	46
III	6	17	nephew	2.2	68	AL	3.6	55
D_1II	3	32	daughter	7.5	35	BK	7.3	36
	4	30	daughter	7.4	35	BR	5.1	45
E_1III	2	25	daughter	4.8	47	LL	—	(50)
H_1III	28	32	son	2.5	64	AN	3.1	59
	29	25	daughter	4.8	47	SH	5.8	42
	30	23	daughter	3.4	56	LB	4.4	49
	31	18	daughter	7.0	36	EJ	—	(50)
II	1	72	brother	3.3	57			
	6	61	brother	3.0	60			
	7	59	brother	3.1	59			
III	1	46	niece	1.1	87			
	2	44	niece	1.5	78			
	3	42	nephew	2.6	63			
	4	40	niece	1.1	87			
	5	37	niece	2.8	61			
	7	30	nephew	1.8	73			
	8	29	nephew	1.9	72			
	9	27	nephew	1.9	72			
	6	36	niece	0.6	89			
	10	2[illegible]	nephew	3.2	58			
	11	19	niece	5.5	43			
	16	43	nephew	2.1	69			
	17	40	nephew	—	(50)			
	12	39	nephew	2.4	66			
	13	41	nephew	2.3	67			
	14	39	niece	3.1	59			
	15	38	niece	4.9				

Relatives Designation according to genealogical tables		Age	Relationship	Serum folates	Deviation points (log serum folates)	Controls: Signum	Serum folates	Deviation points (log serum folates)
I.III	7	44	son	2.0	71	EF	3.9	52
IV	8	19	grandson	5.6	43	GK	5.9	41
	9	18	granddaughter	5.5	43	AL	3.4	56
III	1	47	nephew	2.2	68	BM	2.2	68
	2	41	niece	5.2	45	BA	8.0	33
	5	42	nephew	1.3	82	KL	5.4	44
	4	45	nephew	3.0	60	RE	3.5	55
	6	41	nephew	2.6	63	BW	5.0	46
	3	46	niec	6.8	37	MH	6.3	39
IV	3	16	great-granddaught.	4.5	49	AS	2.9	60
L.II	9	47	sister	3.1	59	AN	—	(50)
	2	59	brother	1.4	8[illegible]	TJ	3.6	55
	4	55	brother	4.1	51	WB	6.8	37
	8	48	brother	3.2	58	EL	3.7	54
	7	50	brother	5.6	43	GV	4.0	5
	11	41	sister	1.8	73	AM	4.5	49
III	6	19	nephew	3.5	55	NP	4.5	49
	7	16	nephew	3.2	58	HEH	7.8	34
P.IV	1	42	son	4.7	47	KLS	3.6	55
V	2	21	grandson	6.4	39	EJ	4.2	50
	1	22	grandson	4.5	49	RS	[illegible]6	63
	3	19	grandson	2.4	66	RS	4.1	(50)
III.I	6	68	brother	4.0	52	BB	2.2	68
	2	56	brother	8.1	33	BG	2.5	64
	4	51	brother	1.8	—	BMH	3.6	55
IV	5	23	nephew	14	8[illegible]	FJ	5.0	46
	4	27	niece	1.7	25	DL	5.8	42
	6	17	nephew	2.0	71	RL	4.8	47
	7	16	nephew	2.0	71	LGR	6.3	39
Q.I	1	70	brother	2.4	65	IN	4.5	50
	8	53	sister	4.9	46	VB	4.0	52
II	6	45	niece	5.0	46	MH	3.5	55
	2	30	niece	2.9	61	MP	5.0	46
III	4	23	great-granddaught.	4.4	49	E[illegible]	3.3	57
	5	21	great-grandson	3.8	53	SeL	4.2	47
T.I	1	80	father	2.5	64	OS	—	(50)
II	2	48	sister	2.9	6[illegible]	VB	4.4	49
	4	47	sister	3.8	53	AML	2.6	63
	5	40	sister	2.7	62	UH	7.9	33

[1]) The proband had earlier had megaloblastic anaemia of pregnancy

[2]) Proband F is not included in the summary of relatives' deviations.

The finding of 70 deviation points concerning the amount of fat in faeces in an examined relative indicates that the relative in question compared with the control person lies on or below the mean average of the amount of faecal fat in the controls plus 2 standard deviations.

Out of 62 examined relatives of sprue patients who have undergone partial gastrectomy 7 show signs of a reduced fat absorption corresponding to at least 70 deviation points. None of the 65 control persons had a deviation point as high as 70 or more.

Judged on the determination of the amount of fat in faeces, the number of relatives with reduced fat absorption of both sprue patients who have not undergone partial gastrectomy and those who have differs statistically significantly from the number of persons with reduced fat absorption among the controls ($p<0.0003$ and $p<0.006$ respectively).

Microbiological folic acid assay of serum in sprue patients' relatives and their controls

The results of microbiological folic acid assay of serum and whole blood in 92 of the above-mentioned sprue material and 68 matched controls can be seen in Table 11

The values for serum folates do not have normal distribution (Hansen 1964) The distribution of the control persons serum folates is skew with a skewness to the left $\left(\frac{m^3}{(\sqrt{m^2})^3} = 0.86\right)$ On the other hand, the logarithms of serum folates do not have skew distribution. The values for the control material agree closely with the normal values provided by the Sahlgrenska Sjukhuset in Göteborg, where the samples were analysed. The mean average value of the logarithms of the values of serum folates in the relatives of the author's sprue patients is significantly lower than the mean average value in the controls ($p < 0.0005$)

From Table 12 it can be seen that there is a significantly lower serum folate concentration in relatives B G H I L, M, O and T compared with the whole control material The values for folate content in serum in the controls were analysed with regard to a possible difference between the sexes and a possible correlation between the

Table 12 Mean average values of log serum folates of sprue patients relative and their controls. Mean differences according to Student t test.

Designation of family	Relatives numbers of	mean of log serum folates	Standard deviation	Differences between the means in families concerned and the mean in all control persons	d.f	p
A	2	0.8940	0.1436			
B	3	0.4445	0.2138	1.9511	70	<0.05
C	12	0.5914	0.1937	0.7712	79	
D	2	0.8722	0.0032			
E	1	0.6812				
G	4	0.4585	0.0916	2.1222	71	<0.01
H	22	0.4239	0.2103	4.8742	89	<0.0005
I	10	0.5340	0.2380	1.6662	77	<0.05
L	7	0.4738	0.2068	2.4049	74	<0.01
M		0.4115	0.1876	1.9061	69	<0.05
N	1	0.5315				
O	2	0.3920	0.1600	2.0819	69	<0.025
P (=F)	10	0.5799	0.2903	0.8311	77	
Q	6	0.5772	0.1272	0.7894	73	
S	1	0.447				
T	4	0.4679	0.0791	2.0130	71	<0.025
U	1	0.4150				
All relatives	89	0.5167	0.2105	Differences between the mean in all relatives and the mean in all control persons	d.f	p
All controls	69	0.6301	0.1395	3.7219	156	<0.0005

*) d.f = degrees of freedom

test result and the person's age. Comparison with the whole control material is considered justified since no difference or correlation could be demonstrated.

Each value of the values of the serum folates in Table 11 has been converted to deviation points by means of the following formula

$$\text{Deviation points} = 50 + \frac{SF - M_C}{SD}$$

SF = logarithm of the current value of the serum folates

M_C = mean average value of logarithms of the serum folates in the controls

SD = standard deviation of logarithms of the serum folates in the controls.

Thus low values of log serum folates, as seen in sprue patients, correspond to a large number of deviation points.

Deviations corresponding to at least 70 deviation points in the determinations of serum folates were demonstrated in 6 out of 35 examined relatives of sprue patients who had not undergone partial gastrectomy and in 15 out of 67 examined relatives of sprue patients who had undergone partial gastrectomy.

The finding of 70 deviation points concerning serum folates level in an examined relative indicate that the relative in question compared with the control persons lies on or below the mean average of the serum folate levels of the control persons minus 2 standard deviations. One of the 68 control persons had a deviation point as high as 70 or more.

The number of persons with reduced serum folate content suggesting impaired folic acid absorption among relatives of sprue patients, both those who have not and have undergone

Table 13. Mean average values of small bowel index in relatives of each of the 17 examined families compared with all the control persons. Mean differences according to Student's t-test.

Family designation	Mean	Standard deviation	n	Differences between the means of families concerned and the mean of all control persons. d f	t	p
Families with probands who had not undergone partial gastrectomy						
A	48.5000	2.1213	2			
C	57.0833	8.5860	12	84	3.4584	<0.0005
F=P						
G	59.2500	6.6520	4	76	2.9101	<0.0025
M	65.0000	14.1421	2	74	3.3049	<0.00025
N	45.00		1			
O	60.0000	15.5563	2	74	2.1808	<0.025
S	73.0		1			(<0.0005)
U	55.0		1			
Families with probands who had undergone partial gastrectomy						
B	56.0000	8.3466	4	76	2.0095	<0.025
D	51.0000	5.6566	2			
E	47.0		1			
H	56.2500	7.6456	24	98	4.0268	<0.0005
I	60.4000	9.2760	10	82	4.6958	<0.0005
L	54.7500	6.1817	8	80	2.0423	<0.025
P	54.9000	11.8457	10	82	2.0515	<0.025
Q	53.3333	10.0928	6	78	1.1845	
T	55.2500	9.3941	4	72	1.6022	<0.1
Controls	50.0945	6.1209	74			

*) d.f. = degree of freedom

of patients registered under code number 286 during the period 1952—1963 were available for study by the author either in the original or in the form of extracts.

The material studied stems from three of the country's seven teaching hospitals during the given period, and from 53 of 98 other hospitals that were usually of standard type or larger. Only patients aged more than fifteen were included. The material from Umeå Hospital was not included.

The above-mentioned case-record material concerned 406 different patients who during the period 1952—1963 were registered under code number 286, in altogether 707 instances of treatment. Among these 406 patients were 163 who were treated under the diagnosis idiopathic sprue or a synonymous term.

In the author's judgement the criteria for the diagnosis idiopathic sprue, given in the Chapter IV dealing with material were satisfactorily fulfilled in 55 cases and largely fulfilled in 39 cases. In 33 cases the author considered that the sprue digagnosis was possible. In the remaining 36 cases, besides sprue or a sprue-like disease, there was another disease which could wholly or partly have caused the reported examination result and the symptoms. Of the 127 patients judged by the author as probably having had sprue, 14 had undergone partial gastrectomy because of peptic ulcer disease, and ten patients had had megaloblastic anaemia in connection with pregnancy. The group with completely or partly fulfilled diagnostic criteria comprised 94 patients. Six of these patients had undergone partial gastrectomy and ten had earlier had megaloblastic anaemia of pregnancy. Of the 94 patients 53 were women and 41 men.

If the studied case record material can be considered to constitute a representative selection, this means that helped partly by the composition of the examined material and partly by the information from the above-mentioned annual reports (a total 1270 instances of treatment registered for cases classified under code number 286 during the given period) the number of cases of diagnosed sprue treated in hospitals throughout Sweden can be calculated to between 96 and 294. The figure 96 was calculated on the basis of those sprue cases in the material which satisfactorily fulfilled the previously given diagnostic criteria, the figure 294 was calculated on the basis of all cases in the material with the diagnosis idiopathic sprue of a synonymous term, and thus corresponds to the figure 163 in the case-record material studied.

On the basis of these figures the author calculated the frequency of diagnosed idiopathic non-tropical sprue in Sweden, among persons aged fifteen or over, to 0.010—0.027 %. If all four groups are included the frequency figure is 0.027 %. The frequency figure gives the number of persons with sprue diagnosis during their lifetime after the age of fifteen.

On studying the above-mentioned case-record material it was not possible to differentiate between those cases which during the period 195_—1963 were newly-diagnosed and those which were diagnosed earlier. In view of this the given frequency figures are too high.

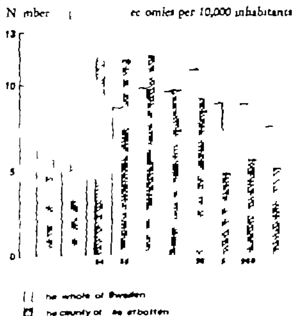
The number of diagnosed cases of idiopathic sprue in the county of Västerbotten during the years 1952—1965 was 20—2 at Skellefteå Hospital and 18 at Umeå Hospital. Two patients in the author's sprue material came from another county. The twenty cases of sprue diagnosed during a 14-year period thus correspond, according to the author's calculation, to a frequency of 0.049 %.

The high frequency of idiopathic sprue in the county of Västerbotten compared with the rest of the country can be due to several factors. Specially great interest has been shown in malabsorption diseases at the medical clinic in Umeå, and patients with malabsorption symptoms who have undergone partial gastretcomy have been paid particular attention. Furthermore, the Västerbotten material also covers the years 1964 and 1965, when it seems that the number of diagnosed cases of idiopathic sprue in the country increased.

The frequency of diagnosed megaloblastic anaemia of pregnancy and puerperium in Sweden and the county of Västerbotten respectively

It was not possible to calculate the occurrence of megaloblastic anaemia of pregnancy in Sweden on the basis of the above-named annual reports to the Social Welfare Board, since the disease was not classified in an uniform way Hansen (1964) found among pregnant women in Göteborg a frequency of megaloblastic anaemia of pregnancy corresponding to 0.087 %. Hansen's diagnostic criteria have been given in the historical survey If his frequency figure can be considered representative for the whole of Sweden, this would mean that about 100 cases of megaloblastic anaemia of pregnancy could be expected per year The occurrence of megaloblastic anaemia of pregnancy in Västerbotten was calculated on the basis of the diagnosed cases of the disease which, registered under different code numbers, have been treated in the county's hospitals. On studying a large number of case-records of patients who during the years 1932—1965 were treated at Skellefteå, Umeå and Lycksele hospitals under different diagnoses such as pernicious anaemia, megaloblastic anaemia and so on, the author found 57 patients with diagnosed megaloblastic anaemia of pregnancy The diagnosis was usually based on the existence of typical bone marrow changes, macrocytic and often hyperchrom anaemia, and on therapeutic response to temporary treatment with maturity factors. The number of cases of diagnosed megaloblastic anaemia of pregnancy in the county of Västerbotten is thus 1 to ? per year The previously given figure of 100 cases per year of megaloblastic anaemia of pregnancy in Sweden corresponds to 0 012 / of the female population. The figure of 1 to 2 cases per year in the county of Västerbotten corresponds to 0.006 % of the female population. The difference between these two percentages is due to differences in diagnostic criteria.

Fig 2 Relative frequency of partial gastrectomy in Sweden and in the county of Västerbotten due to peptic ulcer during the period 1901—1961



The frequency of partial gastrectomy performed because of peptic ulcer disease in Sweden and the county of Västerbotten respectively

The number of partial gastrectomies performed in Sweden and in the county of Västerbotten during the years 1952—1961 on the indication of a peptic duodenal or gastric ulcer was determined with the help of the previously mentioned annual report to the Social Welfare Board, and can be seen in Fig. At the time of the author's study of the material, there was no complete and readily available information concerning the time before 1952 and after 1961

The number of partial gastrectomies performed in the county of Västerbotten during the years 1901—1962 was determined with the help of information obtained from operation reports from the surgical clinics in Västerbotten i.e. at Skellefteå, Umeå and Lycksele hospitals, and can be seen in Fig. 3

Table 16 Summary of case-record details of ten female sprue patients treated in Swedish hospitals[1] other than Umeå, with diagnosed megaloblastic anaemia of pregnancy and puerperium.

Symptoms and observations concerning

I. Idiopathic sprue	Number with the symptoms etc. in question	II. Megaloblastic anaemia of pregnancy and puerperium	Number with the symptoms etc. in question
Intestinal symptoms	10	Anaemia of hyperchrom and/or macrocytic type	10
Loss of weight	3	Megaloblastic erythropoesis	6+1?
Tetany	5	Bone marrow examination not performed because therapy introduced[2]	3
Tendency to bleeding	1	Low serum folates	3
Glossitis	6	Serum vitamin B_{12} 1) normal) low limit value	5
Steatorrhoe	7+1?	Schilling test pathologic 1) without IF	3
Pathological xylose tolerance test	4	2) with IF	1
Flat glucose tolerance curve	3	Favourable response to folic acid only	3
Hypocalcaemia	6	Vitamin B_{12} therapy ineffective	2
Increased activity of alkaline fosfatases	3	Primigravida at time of current pregnancy	6
Hypoprothrombinemia		Multigravida at time of current pregnancy	4
"Deficiency pattern" in X-ray examination	4	Diagnosis made 1) during pregnancy	4
Characteristic findings in biopsy of small intestine	1	2) in puerperium or less than one year after partu	6
Favourable response to gluten-free diet with or without substitution or other therapy	8	Megaloblastic anaemia during further pregnancies	2+2
Diagnosis made 1) before the current pregnancy	2+1?	Megaloblastic anaemia at later time unconnected with pregnancy	2
2) after the current pregnancy	7		
Exacerbation during other than current pregnancy	4		
Sprue symptoms before current pregnancy	5+1?		

[1]) Östersund 1957—1966 Kalmar 1956—1963 Värnamo 1963—1966 Hässleholm 1956—1959 Varberg 196.—1965 Göteborg 1960—1961 Löwenströmska 196., St Erik 1962 Ängelholm 1956—1963 Gävle 1945 Bollnäs 1955—1966 S. Erik 194., Jönköping 1947—1949, Linköping 1960—1961 Katrineholm 1957—1965

[2]) of these patients achieved remission with folic acid therapy the other was under therapy after an earlier diagnosed megaloblastic anaemia.

among 63 women with diagnosed idiopathic sprue The frequency of 9 out of 63 differs significantly ($p<0.0001$) from that which would be anticipated on the basis of Hansen's material from Göteborg (1964)

4) Check up of women who during the period 1931—1965 were treated under the diagnosis megaloblastic anaemia of pregnancy in hospitals in the county of Västerbotten and their matched controls

On scrutinizing the record of the Skellefteå, Umeå and Lycksele hospitals, the author found 57 case-records of women who during the period 1931—1965 were treated at these hospitals under the diagnosis megaloblastic anaemia of pregnancy The disease had been classified according to the WHO system under different code numbers—for example, those corresponding to pernicious anaemia, megaloblastic anaemia, anaemia gravidarum and others. No systematic study of all case-records under the named diagnoses has been made. This applies especially to the study of case-records filed under the diagnosis anaemia gravidarum including to a large extent other commonly occurring forms of anaemia during pregnancy such as anaemia due to an expanded plasma volume and iron deficiency anaemia. It is therefore possible that cases of megaloblastic anaemia of pregnancy treated in Västerbotten hospitals during the period in question, could have escaped the author's notice.

Table 17 Summary of clinical data on women treated at hospitals in the county of Västerbotten during the period 1931—1965 under the diagnosis megaloblastic anaemia of pregnancy and puerperium.

Signum	Age	Number of pregnancies	Number of the pregnancy/pregnancies concerned	Diagnosis made before partus	after partus	Hemoglobin concentration (g%) <5.6	<10.6	Macrocytic and/or hyperchrom anaemia	Bone marrow examination	Free hydrochloric acid proved	Bowel symptom	Glossitis	Tetany	Icterus	Relapse connected or not connected with pregnancy I	II
JA	58	2			+		+	+		+						
SA	42	5	2+4		+	+		+	M	+				+	+	
AGB	47	3	3		+	+		+	M	+	+		+			+
EB	49	1	1	+			+	+	M	+						
EE	41	2	2	+			+		M	+						
BG	37	7	4+5		+	+			M (?)			+			+	
MG	49	4	4	+			+		M							
RH	42	2	1		+		+		M	+						
GH	60	6	3	+		+		+	M (?)	?						
HH	54	7	7		+	+			M			+		+		
MJ	44	4	2		+	+			M	+						
LJ	36	6	5		+		+		M	+						
SJ	68	5	4+5					+							+?	
DK	39	3	3		+	+			M	?	+	+				
HK	42	8	3	+		+		+	M		+					
MK	47	2	1+2	+			+	+	M		+				+	+
DK	57	5	1+2		+		+		M	+	+				+	
AL	45	5	4+5?	+		+		+	M						+?	
SL	43	5	3		+		+	+	M	+	+	+		+		
SL	55	8	6+7?		+	+			M	+					+?	
RL	67	3	1+3?		+	+									+	
MM	39	5	3		+		+		M	+		+				
IN	53	6	6	+			+		m							
AN	49	8	7		+	+		+	M		+					
NN	49	4	4	+			+		M							
MN	39	2	2	+			+		m			+				
HP	62	9	9		+		+	+	M							
GR	42	3	2	+			+		M		+					
ES	62	3	3		+	+		+		+						
AS	54	3	2+3?		+		+	+	M		+				+?	-
IS	61	3	2		+	+		+	M	+						
MW	42	6	5	+			+		M							
SW	37	12	11+12		+	+		+	M			+			+	
AGU	37	2	2		+	+			M	?		+				
RL	44	3	3		+	+			M							
EB	58	4	2	+		+		+	M							+

Key to symbols M = existences of megaloblasts
m = existences of intermediate form of megaloblasts and/or macrocytic myelopoesis.

Table 17 gives clinical data and examination results compiled from case-records of the 36 patients who took part in the present investigation.

The diagnosis was based primarily on the existence of megaloblastic bone marrow changes and characteristic changes in the peripheral blood and the response to treatment with liver preparation, vitamin B₁₂ or folic acid. 31 patients had clear and one patient somewhat unclear maturity deficiency changes in the bone marrow.

In most cases the diagnosis was first made at partus or during puerperium (22 out of 36 cases). Free hydrochloric acid in gastric juice could be demonstrated in fourteen patients.

Megaloblastic anaemia had occurred during another pregnancy in the case of five patients, possibly in a further five also and unconnected with pregnancy in four patients.

Intestinal symptoms described as, for example, diarrhoea, meteorism and flatulence, were found in nine patients, glossitis-stomatitis trouble in eight, icterus in three and tetany in one.

Women with earlier megaloblastic anaemia of pregnancy have on average given birth to more children than the women comprising the control material ($p < 0.05$, $\chi = 4.5$, $v = 1$). No significant difference regarding the number of still-born or malformed children, twin births or abortions experienced could be demonstrated in the above-mentioned groups studied.

Check-ups on 36 of the 57 women who as stated were treated under the diagnosis megaloblastic anaemia of pregnancy were carried out at the medical clinic of Umeå Hospital, on the lines of the examination of sprue patients relatives.

The results of these examinations regarding xylose tolerance test, determination of fat in faeces and microbiological folic acid assay of serum can be seen in Tables 18 and 19.

Regarding xylose tolerance, log amount of fat in faeces and log serum folate content it can be seen from Table 20 that women with earlier megaloblastic anaemia of pregnancy differ significantly from a randomly-selected control material of corresponding age.

Deviations in xylose absorption, amount of fat in faeces and serum folate content in a direction towards that which is usual in sprue cases have been given in the form of deviation points, using the same method as for the sprue patients relatives and their controls (Chapter V 1).

The "small bowel index" (cf. Chap. V 1) was calculated in the examined women with earlier megaloblastic anaemia of pregnancy and in their controls (Table 21). The "small bowel index" is significantly higher ($p < 0.005$) in the women with earlier megaloblastic anaemia of pregnancy than in the controls. Women who had had megaloblastic anaemia of pregnancy earlier thus show deviations from the controls in the same way as patients with sprue.

In the controls the "small bowel index" was analysed with regard to the deviations from the average mean. Out of 34 examined controls 3 deviated from the average mean with a significance of $p < 0.05$.

Out of 36 examined women with earlier megaloblastic anaemia of pregnancy not less than 10 women deviated by a degree corresponding to a deviation in controls from the average mean with a significance of $p < 0.005$. 12 and 8 women deviated with a significance corresponding to $p < 0.01$ and $p < 0.001$ respectively.

Biopsy of the small intestine was carried out on three of the ten women with earlier megaloblastic anaemia of pregnancy who had a specially high "small bowel index" ($p < 0.005$). The examination revealed a flat mucosa in one patient and "convoluted" mucosa in both of the others.

Thus a check-up in the form of inter alia, xylose tolerance test, determination of fat in faeces and determination of serum folate content on 36 women with earlier megaloblastic anaemia of pregnancy often revealed signs of sprue. The women differ significantly thereby from randomly-selected controls of the same sex and corresponding age.

Table 18 Results of xylose tolerance test, determination of fat in faeces, microbiological folic acid assay of serum and calculated "small bowel index" in 36 women who had earlier had megaloblastic anaemia of pregnancy and puerperium.

Sig-num	Age	Amount of xylose urine g per 5 h	Deviation points	Amount of fat in faeces	Deviation points (log f t)	Serum folates ng per ml	Deviation points (log serum folates)	"Small bowel index"
JA	58	6.6	59	5.2	62	1.8	72	64
SA	42	7.9	50	2.2	42	2.4	64	5
AGB	47	4.5	73	3.2	51	—	(50)	58
EB	49	7.9	50	4.0	36	3.8	51	52
EE	41	6.8	57	4.0	56	1.6	75	63
BG	37	4.1	75	8.8	74	3.5	54	68
AG	49	6.9	57	4.0	56	1.8	72	62
RH	42	4.4	73	5.6	64	1.2	83	73
GH	60	6.4	60	2.5	45	3.3	53	53
HH	54	4.1	75	4.4	58	3.6	53	62
MJ	44	8.4	47	4.6	59	1.8	72	59
LJ	36	7.6	52	6.2	66	4.5	47	55
SJ	68	2.1	88	4.4	58	4.3	48	65
DA	39	3.6	78	10.1	79	1.4	79	79
HA	42	8.7	45	11.0	79	1.4	79	68
MK	47	8.4	47	3.1	50	1.2	83	60
DK	57	4.8	71	4.0	56	2.1	68	65
AL	43	6.8	57	5.8	64	3.3	58	60
SL	43	3.6	72	5.5	63	2.8	60	63
SL	55	7.4	53	3.8	53	3.1	57	53
RL	67	8.4	47	10.0	77	3.0	58	61
HM	39	5.1	69	5.2	62	3.7	52	61
IN	53	6.4	60	2.1	41	2.2	66	56
AN	49	3.4	80	13.1	83	0.6	102	88
NN	49	6.3	61	2.9	49	2.3	65	58
HN	39	10.0	36	3.2	51	2.6	62	50
HP	62	3.8	77	3.8	53	1.5	77	70
GR	47	7.3	54	2.1	41	6.1	39	45
ES	62	8.[illegible]	48	4.6	39	1.6	75	61
AS	54	4.5	73	2.6	46	4.8	43	55
FS	41	9.5	39	10.6	78	1.0	88	65
MS	42	7.1	55	4.7	60	6.5	37	51
SW	57	7.1	55	15.0	86	3.5	34	65
AGO	37	6.5	59	3.0	49	2.2	66	58
RL	44	6.2	61	9.2	75	0.8	94	77
EB	58	2.5	86	15.9	87	1.4	79	84

M	= 6.20	$M_{log\ f}$	= 0.6956	$M_{log\ sf}$	= 0.3914
	n = 36		n = 34		n = 35
SD	= 1.98	$SD_{log\ f}$	= 0.2445	$SD_{log\ sf}$	= 0.2269

5) *Analysis of the ques tion of whether the high frequency of partial gastrectomy and megaloblastic anaemia of pregnancy observed in the primary idiopathic sprue material is real or not*

As has been mentioned p eviously where practically all sprue material is concerned it is debatable whether the diagnosis in each single case is satisfactorily supported. This is true not least of sprue patients who have previously undergone partial gastrectomy. Many easons for and pathogenetical mecha nisms in malabsorption conditions after partial gastrectomy can enter the picture, and these can hardly with complete certainty be ex cluded. The author has therefore dealt with the question of whether there are signs of sprue in the relatives of each patient. The

T bl 19 Results of xylose tolerance test, determination of fat in faeces, microbiological folic acid assay of serum and calculated "small bowel index" in 34 controls.

Sig num	Age	Amou t of xylose in urine g per 5 h	Deviation points	Amount of fa in faeces	Deviation points (log f t)	Serum fola es ng per ml	Deviation points (log serum folates)	"Small bowel index
EA	42	7.8	51	5.0	61	4.6	46	53
MA	44	8.6	45	4.8	60	3.0	58	54
NB	60	8.7	45	4.1	57	2.0	69	57
LB	54	8.1	49	4.6	59	13.0	18	42
AB	54	6.4	60	—	(50)	6.8	36	49
LD	49	10.4	33	2.7	47	2.9	61	47
SE	42	5.3	67	3.0	49	5.3	42	53
IE	47	8.3	47	6.0	65	4.0	50	54
NF	39	6.8	57	2.0	4	—	(50)	49
MGF	42	6.7	58	1.5	34	2.7	61	51
MMF	39	6.1	6[illegible]	4.2	57	2.8	60	60
KG	42	9.1	42	1.7	37	4.3	48	42
EG	57	8.8	44	—	(50)	2.8	60	60
ASG	49	9.3	41	2.3	43	2.8	60	48
JH	58	5.7	65	4.[illegible]	57	2.3	65	62
EJ	62	3.3	80	3.1	50	4.7	46	59
GJ	49	8.6	45	3.3	52	4.6	46	48
HL	41	8.3	47	3.7	54	7.4	33	45
VL	47	8.9	43	3.8	55	5.0	44	47
ML	42	8.4	47	1.6	35	2.5	63	48
EL	67	7.7	51	2.4	44	7.0	35	43
NL	57	6.7	58	5.2	62	2.3	65	62
RN	55	7.7	51	5.1	61	4.4	47	53
AMP	37	6.5	59	1.7	37	5.8	40	45
DR	37	6.6	59	1.7	37	4.6	46	47
ES	49	8.3	47	3.9	55	4.5	47	50
ES	62	5.7	65	3.4	52	3.7	52	56
KS	68	7.1	55	1.5	34	4.3	47	45
EV	45	6.3	61	3.8	55	1.4	79	65
AU	61	5.4	67	—	(50)	3.8	51	46
EO	53	6.6	59	1.5	34	—	(50)	48
AMJ	41	7.3	54	5.5	63	7.8	32	50
HM	39	7.4	53	7.5	70	14.4	18	47
GM	36	9.4	40	—	(50)	7.0	35	42

M	= 7.48	$M_{log\,f}$	= 0.4984	$M_{log\,sf}$	= 0.5842
n	= 33	n	= 30	n	= 31
SD	= 1.45	$SD_{log\,f}$	= [illegible].2061	$SD_{log\,sf}$	= 0.1830

Table 20 Mean average values of xylose tolerance, log amount of faecal f t, log content of serum folates in women who earlier had had megaloblastic anaemia of pregnancy and in their matched controls, and mean differences according to Students t-test.

	Women who earlier had had megaloblastic anaemia of pregnancy			Controls			Mean differences according to Studen t test		
	Mean	Standard deviation	n	Mean	Standard deviation	n	t	d.f	p
Amount of xylose in urine (g per 5 hours)	6.2000	1.9837	36	7.4818	1.4516	30	3.0414	67	<0.0025
Logarithm of the amoun of faecal f (g per 24 hours)	0.6956	0.[illegible]445	36	0.4984	0.[illegible]61	30	3.5034	64	<0.0025
Logarithm of conten of serum folates (ng per ml)	0.3914	0.[illegible]269	35	0.5842	0.183	31	3.7720	64	<0.0005

[1]) d.f = degree of freedom

Table 1 "Small bowel index" in women, who earlier had had megaloblastic anaemia of pregnancy and their matched controls. Numbers of individual women with high "small bowel index" indicated with reference to the significance of corresponding deviation from mean of the controls.

Signum	"Small bowel index"	p ≤ 0.001	p ≤ 0.005	p ≤ 0.01	p ≤ 0.05	"Small bowel index"	p ≤ 0.001	p ≤ 0.005	p ≤ 0.01	p ≤ 0.05
Women with earlier megaloblastic anaemia of pregnancy:						Control				
IA	65			1		53				
SA	52					54				
AGB	57					57				
EB	52					42				
EF	62				1	49				
BG	73	1				47				
MG	61				1	53				
RH	74					54				
GH	53					49				
HH	62				1	51				
MJ	59					60				
LJ	57					42				
SJ	63			1		60				
OK	86	1				48				
HK	77					62				1
MK	59					59				
DK	65			1		48				
AL	61				1	45				
SL	66		1			47				
SL	54					48				
RL	68		1			43				
MM	62				1	62				1
IN	55					53				
AN	122	1				45				
NN	57					47				
HN	49					50				
HP	69	1				56				
GR	44					45				
ES	61				1	65			1	
AS	54					46				
FS	77	1				48				
MW	51					50				
SW	83	1				47				
AGU	57					42				
RL	83	1								
EB	103	1								
$M_{m.a.p.}$ = 62.3885						M = 50.7941				
$SD_{m.a.p.}$ = 9.3944						SD = 6.2851				
n = 36						n = 34				

Difference between the mean of "small bowel index" in women, who earlier had had megaloblastic anaemia of pregnancy and that in controls is statistically significant ($p < 0.0005$, $t = 6.0732$; degree of freedom = 68).

*) One year later carcinoma coli was diagnosed in this patient.

demonstration of sprue or signs of sprue in the relatives indicates that the patient belongs to a sprue family and this is considered to establish the patient's sprue diagnosis.

On examining relatives of the nine sprue patients who had undergone partial gastrectomy the author was able to demonstrate that they deviated significantly from the corresponding controls in xylose tolerance, amount of fat in faeces and serum folate content. The relatives showing these significant differences belonged to seven families. For relatives of nine sprue patients who had not undergone partial gastrectomy the corresponding figure is six. It should be noticed that in connection with the nine sprue patients who had not

undergone partial gastrectomy 35 relatives were examined. The corresponding figure for relatives of the nine sprue patients who had undergone partial gastrectomy is 69 Thus more relatives of sprue patients who had undergone partial gastrectomy were examined than of those who had not. The author s finding that six out of eleven sprue patients who had not undergone partial gastrectomy had demonstrated sprue in the family is not therefore directly comparable with the finding that seven out of nine sprue patients who had undergone partial gastrectomy had sprue in the family

Out of the author s twenty patients with diagnosed idiopathic sprue nine had previously undergone partial gastrectomy i.e a relative frequency of 45 per cent. If for the diagnosis idiopathic sprue proof of the familial occurrence of sprue also is required, the corresponding frequency is seven out of thirteen or 54 per cent.

It is, however apparent that if the six sprue patients with demonstrated sprue in the family who had undergone partial gastrectomy are placed against the total number of twenty of the author s sprue patients a too low figure, or at any rate a not too figure, is obtained for the relation between sprue patients who had undergone partial gastrectomy and the total number of sprue patients.

Two of the author s sprue patients were not from the county of Västerbotten One belonged to the group who had undergone partial gastrectomy the other to the group which had not undergone partial gastrectomy In both cases sprue was demonstrated in the family

The author has previously dealt with the frequency of partial gastrectomy in Sweden and the county of Västerbotten, and intends further to place the frequency of partial gastrectomy in his sprue material in relation to the frequency of partial gastrectomy in the county of Västerbotten. In the continued analysis of the author s sprue material it is therefore necessary partly to withdraw the two sprue patients who were not from Västerbotten and partly to add two patients whose sprue was diagnosed and treated at Skellefteå Hospital. Relatives of the latter patients were not examined. Neither of these same two patients had undergone partial gastrectomy

On the basis of the accumulated frequencies of partial gastrectomy according to Table 15 and the mean population in the respective 5-year groups, the anticipated frequency of partial gastrectomy in this diagnosed sprue material in Västerbotten can be calculated as 1 98 %$\pm$0 18 %.

The observed frequency of six partial gastrectomy cases out of twenty sprue patients differs significantly from the anticipated frequency which is maximally 2.52 % ($p<0\ 001$) The figure 2.52 corresponds to the previously given partial gastrectomy frequency of 1 98 plus 3 times the standard error If the demand for demonstrated familial sprue in the families of patients who have undergone partial gastrectomy is relinquished, the corresponding figure becomes eight out of twenty and the significance of the deviation from the anticipated partial gastrectomy frequency is higher

The author has previously found that the frequency of diagnosed sprue in Sweden between 1957 and 1963 amounts to 0 027 % of the adult population over fifteen years of age. This figures refers to a combination of all groups of diagnosed sprue in the author s earlier classification of the sprue material in question. The groups were as follows: satisfactorily fulfilled diagnostic criteria largely fulfilled diagnostic criteria possible but not verified sprue diagnosis, and sprue or sprue like conditions where another disease existed which could wholly or partly have caused the reported symptoms and the examination results The frequency figure is thus the highest which can be put forward. This frequency figure includes both newly diagnosed cases and some which were diagnosed before the period in question, and is thus, even in view of these facts, too high

as a measure of the frequency of diagnosed sprue.

As has been stated earlier the frequency of diagnosed sprue in the county of Västerbotten during the period covered by this investigation is higher and the reasons for this have already been discussed.

The frequency of diagnosed sprue in the four most northerly counties, with the exception of Västerbotten, has been calculated for the period in question it is noticeably lower than the national average

On the basis of the calculated frequency of diagnosed sprue in Sweden, 0.027 %, the number of diagnosed sprue cases in Västerbotten should be 45 If that sprue material corresponded to the author's above discussed material regarding the patients date of birth, year of diagnosis and sex one would expect to find among those 45 sprue patients a partial gastrectomy frequency of maximally 2.52 %, i.e. less than one sprue patient who had undergone partial gastrectomy The anticipated frequency of partial gastrectomy for the whole population over fifteen years of age in Västerbotten is, however lower 1.00 / ±0.07%/ i.e. maximally 1 6%/ The demonstration of six sprue patients in Västerbotten who have undergone partial gastrectomy differs significantly from the anticipated frequency in both cases ($p < 0.001$)

In the case of both the above calculation methods, the finding of six sprue patients in the stated material who have undergone partial gastrectomy is higher than the anticipated frequency and indicates a connection between sprue and earlier partial gastrectomy

On the basis of Hansen's investigation in Göteborg (1964) the frequency of megaloblastic anaemia of pregnancy in Sweden is found to be 0 011 / of the adult female population over fifteen years of age. The author found that the frequency in Västerbotten amounts to 0 006 %. The difference between these two figures has been discussed earlier

In the author's idiopathic sprue material consisting of ten women two had had megaloblastic anaemia of pregnancy In the previously described study of case-records of sprue patients treated in Swedish hospitals, the author found details of ten more female sprue patients who had had megaloblastic anaemia of pregnancy This figure of ten refers to 53 female sprue patients On the basis of a frequency of megaloblastic anaemia of pregnancy corresponding to 0 011 % of the female population over fifteen years of age, it is found that the observed frequency of megaloblastic anaemia of pregnancy among patients with diagnosed sprue in Västerbotten and Sweden differs significantly from the anticipated frequency ($p < 0.001$ and $p < 0.001$ respectively)

VI GENERAL DISCUSSION

Of the author's 20 sprue patients, nine had earlier undergone partial gastrectomy It has been emphasised previously that in practically all sprue material it is debatable whether the diagnosis in each single case is satisfactorily supported. This is true of the author's material also, and especially of those patients who had earlier undergone partial gastrectomy It was considered therefore important to support the sprue diagnoses by demonstrating if possible the existence of sprue or signs of sprue in the families of the patients in question

An account of previous investigations into the familial occurrence of sprue is given in the literature survey (Table) These deal

largely with the investigation into relatives of patients with coeliac disease of childhood. Investigations into relatives of adult patients with idiopathic non-tropical sprue are reported only by Davidson and Fountain (1950) and MacDonald and colleagues (1965) The method of procedure in the latter ex aminations has been described earlier The investigations must be said to be relatively incomplete. Furthermore, there is a lack of adequate control material

The author carried out examinations of the relatives of his sprue patients. The material was described in Chapter IV methods of procedure results and analysis of resultsin Chapter V 17 families represented 18 sprue patients and 94 relatives were examined regarding xylose tolerance, amount of fat in faeces and serum folate content. The control material consisted of 74 persons. These control persons corresponded to the relatives in the matter of sex and age, with reference essentially to relatives in 16 of the 17 families. The results of the different above-mentioned tests on the controls were analysed with regard to a possible difference between the sexes and a possible correlation between the test result and the age of the persons ncerned. No difference or correlation could demonstrated, so comparison between single families or single persons in the families and the whole control material was considered justified.

The examined relatives seen as a group differ noticeably and statistically significantly from the controls in the way that patients with idiopathic sprue differ from normal persons. 11 of the 18 different families investigated differed statistically significantly from the controls. 6 of those 11 families related to sprue patients who had not undergone partial gastrectomy and 5 to patients who had undergone the operation. Of the 94 examined relatives, 17 differed significantly from the controls ($p < 0.005$) These 17 persons belonged to 13 families—6 families with sprue patients who had not undergone partial gastrectomy and 7 families with sprue patients who had. The explanation for significant deviations in 11 out of 18 examined families when the families were compared with the controls, and in 13 out of 18 examined families when the individual members were compared with the controls, lies in the fact that the statistical processing was not the same in both cases. It should be pointed out that of the 17 persons mentioned who differed significantly from the controls, only a small numbers had subjective complaints of the type characteristic of sprue patients. Persons belonging to a family where confirmed idiopathic non-tropical sprue exists, who themselves show signs of sprue without actually having any appreciable subjective sprue symptoms, will be called henceforth persons with latent idiopathic sprue.

Systematic examinations of idiopathic sprue patients relatives under standardised con ditions and with the use of control material, have not, as far as the author has been able to discover been made previously On the basis of 18 examined families with idiopathic sprue, the author found that among the patients relatives 17 persons deviated significantly from the controls. The number of relatives examined was 94 Thus 18 % of the relatives deviated from the controls. Earlier researchers into the question of the familial occurrence of coeliac disease of childhood and idiopathic sprue in adults have found signs of sprue in 0 1—19 % of the relatives examined (Table 2) The probands usually consisted of children with coeliac disease of childhood. In Davidson and Fountain s material (1950) the patients were 75 adults with idiopathic steatorrhoea. They found a sprue frequency of 4 % in the relatives. Theirs seems to be the largest material where work has been based on adult probands.

Of the author's 20 sprue patients, 10 were women. 2 of these had earlier had megaloblastic anaemia of pregnancy The high frequency of megaloblastic anaemia of pregnancy in this sprue material is remarkable, and has formed the basis of an analysis of the question

of a possible connection between megaloblastic anaemia of pregnancy and idiopathic non-tropical sprue. Whitfield (1967) has maintained that there is a connection between tropical sprue and megaloblastic anaemia of pregnancy. He observed that among 57 patients with megaloblastic anaemia of pregnancy 13 had tropical sprue. The disease had in these cases been discovered in the later stages of pregnancy. Both the megaloblastic anaemia of pregnancy and the sprue were favourably affected by the treatment including administration of folic acid. The observation was interpreted as meaning that folic acid deficiency in connection with pregnancy causes, changes in both the bone marrow and the gastro-intestinal tractus. Lawrence and Klipstein (1967) have made similar observations concerning patients from the Caribbean archipelago with megaloblastic anaemia of pregnancy.

According to several authors the response to folic acid treatment in patients with tropical sprue is variable (cf. Baker et Mathan 1968). Treatment with adequate amounts of folic acid seems to often cure the megaloblastic anaemia and other signs of folic acid deficiency but evidence of consistent improvement upon intestinal function is lacking (Baker et Mathan 1968).

In the discussion about the pathogenesis of megaloblastic anaemia of pregnancy it has been suggested that these patients have a special constitution. In support of this opinion the arguments have been put forward that there is a tendency for a relapse of the disease to occur in another pregnancy. In these patients megaloblastic anaemia have also been described as occurring without any connection with pregnancy. It has further been stated that blood group A is more common in patients with megaloblastic anaemia of pregnancy than in the rest of the population.

Patients with megaloblastic anaemia of pregnancy always seem to have a reduced amount of folic acid in the blood. Patients with idiopathic sprue often have a reduced amount of folic acid in the blood. Patients with megaloblastic anaemia of pregnancy have only to a limited extent been examined with regard to symptoms that are characteristic of idiopathic non-tropical sprue. Giles (1958, 1966), however, has described steatorrhoea as being relatively common among patients with megaloblastic anaemia of pregnancy. Rare cases of megaloblastic anaemia of pregnancy with reduced xylose absorption have also been described. Details of these investigations can be found in Table 4.

As far as the present author has been able to find, it has not been maintained that megaloblastic anaemia of pregnancy develops from the basis of a sprue disease. Giles (1966), however, considers that reduced absorption of folic acid can almost certainly be a pathogenetical factor in megaloblastic anaemia of pregnancy. He found that 4 out of 9 healthy pregnant women had lower folic acid absorption than non-pregnant women. The corresponding figure was 11 out of 11 for women with megaloblastic anaemia of pregnancy. 9 out of 11 women with megaloblastic anaemia of pregnancy had reduced folic acid absorption compared with healthy pregnant women. Giles, however, did not suggest the sprue diagnosis in these patients. Similar observations have been reported by other authors. Hansen (1964), on examining folic acid absorption in women with megaloblastic anaemia of pregnancy, found that 2 out of 6 examined women had reduced absorption. He did not, however, attach any significance to this, but assumed that the megaloblastic anaemia of pregnancy was caused by a defect in the folic acid metabolism.

In Chapter V the author analysed the high frequency of megaloblastic anaemia of pregnancy partly in his own material of female sprue patients and partly in a sprue material obtained by studying case-records of sprue patients treated in other hospitals in Sweden. In both cases he showed that the frequency of megaloblastic anaemia of pregnancy in female sprue patients is statistically significantly higher than in the normal population. The author described in the same

chapter a check up using xylose tolerance test, determination of the amount of fat in faeces and determination of serum folate content, on 36 women who 8—37 years previously had had megaloblastic anaemia of pregnancy the women often showed signs of sprue, and the results statistically significantly differ from those shown by a randomly-selec ted control material of the same sex and of corresponding age.

The question then arises of whether these women s reduced absorption demonstrated by the author was the cause of their "megaloblastic anaemia in pregnancy" by way of a reduced absorption of maturity factors, espec ialy folic acid or whether a supposed folic acid deficiency during pregnancy could possi bly cause small intestine damage that gives rise to an established malabsorption.

With the aid of small intestine biopsy Herbert (1962), Gough et al. (1963), Forshaw et al (1964) and Winawer et al (1965) studied the morphology of the small intestine mucosa of patients with nutri tional folic acid deficiency They found no evidence of small intestine changes typical of idiopathic sprue Butterworth and Perez Santiago (1958) ten Thije 1963 and Sheehy 964) however observed "megalocytic" ıanges in the epithelium of the small intes tinal mucosa in patients with a probable nutritional deficiency of folic acid.

The question of whether nutritional deficiencies of maturity factors can bring about reduced absorption has recently been arisen (cf Matthews 1967) Most authors have hitherto found little or no evidence of a reduced intestinal absorption in patients with nutritional folic acid deficiency (Herbert 1962 Veeger et al. 1965 among others) As diagnostic aid in recognising megaloblastic anaemia caused by nutritional folic acid deficiency it is also recommended to use absorption test in ruling out malabsorption (Sullivan 1967) Thus it is not probable that folic acid per se could occasion small intestine changes typical of idiopathic sprue such as pathologically anatomical changes and reduced absorption

Regarding the above-mentioned 12 women with the combination of megaloblastic anaemia in an earlier pregnancy and idiopathic sprue (Chap V), it is true that the symptoms of sprue were present before the pregnancy in question in 7 or 8 women. In the case of remaining 4 or 5 nothing was known about the time-lapse between the sprue symptoms and the megaloblastic anaemia in pregnancy The observation that sprue symptoms were found before the actual pregnancy argues definitely against the fact that general reduction of intestinal absorption, demonstrated by the present author in the examined group of women with earlier megaloblastic anaemia of pregnancy could be caused by means of folic acid deficiency in connection with mega loblastic anaemia of pregnancy

Only a few authors have dealt with the question of how a pregnancy affects the course of idiopathic sprue. Cooke et al. (1953) was unable to observe among 32 female idiopathic sprue patients, one single case of obvious exacerbation during pregnancy Green and Wollaeger (1960) observed, among 24 female sprue patients, an improvement in four during pregnancy but an obvious exacer bation in the others. None of these authors, however followed up these patients with regard to the occurrence of megaloblasts in the bone marrow or the folic acid content in the blood. Since the administration of a cortisone-type preparation favourable influences the progress of sprue disease, the supposition presents itself easily that the changed hormone metabolism connected with pregnancy can be significant for the course of both manifest and latent sprue.

In the author s material 3 women with earlier megaloblastic anaemia of pregnancy and with abnormal values for xylose absorption, amount of fat in faeces and serum folate content were examined by means of biopsy of the small intestine. In one case a flat mucosa was revealed, and in two cases mucosa with "convoluted appearance"

Demonstrations of small intestine biopsies typical of idiopathic sprue in a number of women with earlier megaloblastic anaemia of pregnancy are of great interest in the earlier discussion about connection between megaloblastic anaemia of pregnancy and idiopathic sprue. As previously mentioned, other authors found no evidence of small intestine changes of sprue-type in studied patients with nutritional folic acid deficiency Thus the present author s demonstration of small intestine biopsies of sprue-type gives therefore support to the opinion that in the determined connec tion between idiopathic sprue and megaloblastic anaemia it is the idiopathic sprue that is the primary cause.

A previously-described study of case-records of sprue patients treated in Swedish hospitals during the period 1952—1963 revealed ten female sprue patients who earlier had mega loblastic anaemia of pregnancy (Table 16) It can be seen from the Table that in 5 of those 10 cases there are details of tetany in connection with pregnancy Megaloblastic anaemia and even tetany are relatively common in cases of idiopathic sprue As the author has shown above, megaloblastic anaemia often becomes manifest in sprue patients in connection with pregnancy Analogously the supposition may easily be found that pregnancy in a sprue patient can make a tetany manifest.

The observations given by earlier authors as support for the view that patients with megaloblastic anaemia of pregnancy have special constitution can be explained by the demonstrated high frequency of manifest or latent idiopathic sprue in patients with mega loblastic anaemia of pregnancy The present author's material does not allow any conclusions to be drawn concerning the question of whether megaloblastic anaemia of pregnancy always develops from the basis of idiopathic sprue or some other malabsorption condition with reduced folic acid absorption. As previously stated, sprue disease does not follow an even course, but it entails both exacerba tions and remissions. An analysis of how often idiopathic sprue forms the basis of megaloblastic anaemia of pregnancy would require the patients with megaloblastic anaemia of pregnancy to be followed up for long periods regarding sprue symptoms. The question of whether the folic acid content of food s significant for the development of megaloblastic anaemia of pregnancy in such countries as Sweden, other than in connection with, for example, manifest or latent sprue must for the time being be left open

A possible connection between partial gas trectomy and idiopathic sprue has been dis cussed by earlier authors. As mentioned in the historical survey several authors have described sprue in patients who have und r gone partial gastrectomy and put forward the idea that the sprue became manifest through the partial gastrectomy (Table 5) As far as the present author has been able to find, however no-one has previously tried to analyse this relationship in any detail In surveys of malabsorption conditions after partial gastrectomy there is usually no men tion of a possible connection between partial gastrectomy and sprue — or att least this question occupies a very modest position (cf Stammers & Williams 1963).

On the basis of his sprue material of 20 patients, of whom 9 had undergone partial gastrectomy the author has tried to analyse the relationship in detail. As malabsorption after partial gastrectomy is rela tively common since it can be assumed to be brought about in several different ways, and as the differential diagnosis between different malabsorption conditions is often uncertain n each individual case, the author has attempted to support the sprue diagnoses by examining the patients relatives with regard to the possible existence of sprue or signs of sprue. The majority of the author's sprue patients came from the county of Västerbotten. The author placed the partial gastrectomy frequency found among his sprue patients in relation to the partial gastrectomy frequency in Västerbotten area. Further the frequency of diagnosed idiopathic sprue in Sweden was

calculated. On the basis of that figure the anticipated number of diagnosed idiopathic sprue cases in the county of Västerbotten was calculated. Based on these figures, and on the anticipated partial gastrectomy frequency a calculation was made of the anticipated number of cases of sprue patients who had undergone partial gastrectomy within the area in question. That value obtained refers to the supposition that there is no connection between sprue disease and partial gastrectomy The number of cases calculated in this way were placed in relation to the number of cases demonstrated by the author

On examining, with regard to xylose tolerance amount of fat in faeces and serum folate content, relatives of sprue patients who had undergone partial gastrectomy and in corresponding examinations of a control material the author found, as stated earlier in this discussion, that 5 out of 9 families differed statistically significantly from the controls (Table 13) Of the 69 examined relatives of the sprue patients who had undergone partial gastrectomy 11 persons differed statistically significantly from the controls (Table 14) These 11 persons belonged to 7 different families. The reason for significant deviations being found in 5 out of 9 families when the families were compared with the controls, and in 7 out of 9 families when individual family members were compared with the controls, has been dealt with earlier Thus in the case of 7 of the 9 sprue patients who had undergone partial gastrectomy it was possible to confirm the sprue diagnosis by examining their relatives.

Concerning the diagnosis idiopathic sprue in patients who have undergone partial gastrectomy it should be observed that interpreting the results of carbohydrate tolerance tests in such patients can cause difficulties. The pattern of an early high peak in blood sugar after glycose tolerance test in patients who have undergone partial gastrectomy is well known (Boller 1947 Amdrup et al 1966 and others) Similar curves are obtained from xylose tolerance test also (Merian 1967 Hess Thaysen 1963 and others) It is likely that this circumstance is caused by the loss of pyloric function in partial gastrectomy patients. The author found that intraduodenal administration of xylose to normal persons resulted in higher serum concentrations and larger amounts of xylose recovered in urine than did intragastric administration of the xylose. The rate of administration was on both occasions the same. The author found the same situation in the corresponding examination of sprue patients. As an example of this may be cited one sprue patient (patient L, Table 6) who after intragastric administration of xylose had an average five-hour excretion in urine of 3 g xylose. After intraduodenal administration of xylose the corresponding figure was 5 Thus there is reason to suppose that where there is damage of the small intestine in both patients who have undergone partial gastrectomy and those who have not, examination with oral xylose tolerance test will result in values indicating such intestinal damage less often in the case of those who have undergone the operation than in the care of those who have not. A comparison of the results of the xylose tolerance test in both the author's sprue patients who had undergone partial gastrectomy and those who had not shows that the excretion in urine was lower in the latter than in the former (Table 6) This is probably because of the above-mentioned mechanism.

As previously stated, the author placed the partial gastrectomy frequency found among his sprue patients in relation to the partial gastrectomy frequency in the county of Vasterbotten. The results were reported and analysed in Chapter V The partial gastrectomy frequency observed in the author's sprue patients was corrected to allow for the fact that not all patients came from Västerbotten. The results showed that the partial gastrecomy frequency in the author's sprue patients was higher than the anticipated frequency and that the difference was statistically significant ($p<0.001$). This was true regardless of whether the demand was laid down or not

for confirmation of the sprue diagnosis in patients who had undergone partial gastrectomy through the demonstration of the existence of sprue in the patients families.

Further the frequency of diagnosed idiopathic sprue in Sweden was calculated From that figure the anticipated number of diagnosed idiopathic sprue cases in Västerbotten was calculated. On the basis of these figures and the anticipated partial gastrectomy frequency the author calculated how many sprue patients who had undergone partial gastrectomy one could expect to find within the area in question if there were no connection between sprue disease and partial gastrectomy The calculated number of cases was placed in relation to the number of cases demonstrated by the author an account of the results is given in Chapter V The author demonstrated 8 sprue patients in Västerbotten who had undergone partial gastrectomy In 6 of these 8 cases the sprue diagnosis was confirmed by demonstrating the existence of sprue in the families of the patients concerned. The anticipated number of diagnosed idiopathic sprue cases in Västerbotten was calculated as being 45 Using as reference points this figure and the anticipated partial gastrectomy frequency it can be calculated that at the most one of these cases can be expected to have undergone partial gastrectomy As has been stated, the demonstrated number of patients with confirmed sprue diagnosis who had undergone partial gastrectomy was 6 The difference is statistically significant ($p<0\ 001$)

The author has previously mentioned that earlier researchers have described sprue in patients who have undergone partial gastrectomy ,and have put forward the idea that the sprue became manifest through the partial gastrectomy Such an interpretation would completely explain the result the author has obtained from an analysis of a large number of such patients.

Patients who have undergone partial gastrectomy can, however be expected to seek medical advice and to be admitted to hospital more often than others. The question must therefore be asked whether the demonstrated connection between sprue and partial gastrectomy applies in fact to only a selection from the whole group of patients in Västerbotten who have undergone partial gastrectomy The anticipated number of sprue patients in Västerbotten to have undergone partial gastrectomy was calculated by the author as less than one. In making this calculation the author s reference points were the anticipated frequency of diagnosed sprue and the anticipated frequency of partial gastrectomy The observed number was 6—a statistically significant difference, as has been pointed out. The suggested explanation can thus be withdrawn from the discussion.

The question can also be raised of whether the demonstrated connection between sprue and partial gastrectomy is due either to the fact that peptic ulcer disease is more common in sprue patients than the rest of the population or to the fact that patients with both peptic ulcer disease and sprue have more pronounced complaints than patients with only ulcer disease, and therefore undergo partial gastrectomy to a greater extent than do the latter From a study of the relevant literature, the author has been unable to find any basis for a connection between peptic ulcer disease and sprue. No evidence for such a connection is provided by malabsorption examinations and small intestine biopsy in ulcer patients who have not undergone a gastrectomy (Wollaeger et al. 1946 Christiansen et al. 1959 Leuthold et al 1964 and others) Supposing an ordinary frequency of peptic ulcer (<10 /) among sprue patients it is unprobable to expect in Västerbotten 6 sprue patients gastrectomised according to the second alternative.

The author considers therefore that the de- demonstrated connection between idiopathic non-tropical sprue and partial gastrectomy is due o the fact that the sprue can become manifest through the partial gastrectomy

If the argument is accepted that sprue disease can become manifest through partial gastrectomy it is of course of interest to

know how this can come about. For the present this question can only be the subject of speculation. The connection between sprue and deficient digestion of gluten is discussed in the historical survey Chapter II. If the harmful effect of gluten is assumed to be caused by a congenital or acquired defect in enzymatic gluten digestion of the gastro-intestinal tracts, the supposition easily presents itself that partial gastrectomy can reduce the activity of the gluten digestion effect of the enzymes of the gastro-intestinal tractus.

Concerning the quantitative significance of the demonstrated connection between sprue and partial gastrectomy the following can be stated. *The author observed in the county* of Västerbotten, with a population corresponding to roughly one thirtieth of the whole population of Sweden, eight patients with idiopathic sprue who had undergone partial gastrectomy If the demand is laid down for confirmation of the sprue diagnosis by the demonstration of sprue or signs of sprue among the patients' relatives, the total is 6 The diagnoses concern the years 1959—1965 Re-calculated for the total Swedish population of about 7,5 million, the annual total of sprue patients who have undergone partial gastrectomy becames 34 and 25 respectively These figures are possibly too high, since among other things they relate to a period when there was a high frequency *of partial* gastrectomy

VII SUMMARY

During the period 1952—1965 20 patients were treated [illegible] the medical clinic of Umeå Hospital under the diagnosis idiopathic non tropical sprue 1[illegible] of the patients were women, [illegible] of wh[illegible]m had earlier had megaloblastic anaemia of p[illegible]nancy 9 of the 20 patients had undergone partial gastrectomy The number of patients who had earlier had megaloblastic anaemia of pregnancy or undergone partial gastrectom[illegible]s remarkably high.

In the historical survey an account is given of tropical sprue, coeliac disease of childhood and idiopathic non-tropical sprue Similarities and differences between these conditions are described. Previous investigations into the familial occurrence of the last two conditions are also described. An account is given of megaloblastic anaemia of pregnancy in which works on the pathogenesis of megaloblastic anaemia of pregnancy are discussed in particular. Literature dealing with malabsorption after partial gastrectomy is described and analysed with particular regard to details of intestinal changes.

94 relatives of the above-mentioned patients with idiopathic sprue were examined for signs of sprue. The relatives represented 17 different families. As well as the relative material, a randomly-selected control material corresponding to the latter in age and sex was examined in a similar way The control material consisted of 74 persons. The examinations included, inter alia xylose tolerance test, determination of fat in faeces and microbiological determination of serum folate content. The examined relatives differed as a group noticeably and statistically significantly from the controls in the way that patients with idiopathic sprue differ from healthy persons. 17 relatives differed significantly from the controls. These 17 persons belonged to 13 families. Only a few of them had subjective complaints of the type characteristic of sprue patients.

In a study of case-records of sprue patients treated in other Swedish hospitals (apart from Umeå Hospital) among 53 women 10 cases of earlier megaloblastic anaemia of pregnancy and puerperium were found. The high frequency of megaloblastic anaemia of pregnancy in this material, as in the author's own material of female sprue patients, is remarkable. In both groups the frequency of megaloblastic anaemia of pregnancy is considerably higher than and statistically significantly different from, that of the normal population

A check-up using the above-mentioned malabsorption tests on 36 women who 8—37 years earlier had had megaloblastic anaemia of pregnancy showed that they often had signs of sprue, and that they differed statistically significantly from a female control material of corresponding age. The observations presented by earlier authors as support for the view that patients with megaloblastic anaemia have a special constitution can be explained by the high frequency of manifest latent idiopathic sprue in patients with earlier megaloblastic anaemia of pregnancy The significance of the demonstrated relationship is discussed.

9 of the author's 20 sprue patients had undergone partial gastrectomy As stated earlier this partial gastrectomy frequency is remarkably high. Where practically all sprue material is concerned, it is debatable whether the diagnosis in each single case is satisfactorily supported the sprue patients relatives were therefore examined, using the above-mentioned malabsorption tests, with the aim of demonstrating if possible a familial occurrence of sprue The need to attempt confirmation of the sprue diagnoses was considered particularly important in the case of sprue patients who had undergone partial gastrectomy The demonstration of sprue in a patient's family was considered to confirm the patient's sprue diagnosis. The existence of signs of sprue was demonstrated in the families of seven of the nine sprue patients who had undergone partial gastrectomy The frequency of partial gastrectomy in the county of Västerbotten was calculated with regard to sex, year of birth and calender year The partial gastrectomy frequency among the author's sprue patients from Västerbotten is significantly higher than the anticipated frequency This is true even if the demand is laid down for confirmation of the sprue diagnosis in patients who have undergone partial gastrectomy through the demonstration of sprue in the families of the patients concerned.

The frequency of diagnosed idiopathic sprue in Sweden was calculated. On the basis of the figure obtained, the anticipated number of diagnosed idiopathic sprue cases in Västerbotten was calculated. From this reference point, and from the calculated partial gastrectomy frequency the anticipated number of sprue patients within the area in question who had undergone partial gastrectomy was calculated The number was at the most one. This figure is in keeping with the assumption that there is no connection between sprue and partial gastrectomy The demonstrated number of sprue patients in Västerbotten who have undergone partial gastrectomy is higher and the difference is statistically significant.

The reason for the demonstrated connection between idiopathic sprue and partial gastrectomy is discussed. The author considers the reason to be that the sprue can become manifest through the partial gastrectomy

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Supplementum 509

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RETENTION OF ORALLY ADMINISTERED ^{47}CALCIUM IN MAN UNDER NORMAL AND DISEASED CONDITIONS STUDIED WITH A WHOLE-BODY COUNTER TECHNIQUE

by

Hans Erik Sjöberg

Orsa 1970

Ab Bröderna Ohlséns tryckeri Orsa 1968

This thes is based on the following papers

I Retention of rally administered ^{47}Ca in man measured in a wh le-body counte
Scand J clin Lab Invest 1970 in press Togethe with P R Izen-st in and E Arman

II Retention afte orally administered ^{47}Calcium in patients after gastrectomy
Am r J dig Dis 12 1166 1967 Together with P R Izenstein

III Retention f ral ^{47}Ca in patients with intestinal malabsorption Regional ent ritis and pancreatic insufficiency
Scand J Gastroent 1970 in pres Togethe with L H:son Nilsson

IV Retention of ^{47}Calcium administered orally patients with primary hyper-parathyroidism
Horm metab Res 2 32 1970

V Retent on f ral ^{47}Calcium in acromegaly
Horm metab Res 1 136 1969

VI Retention f ral ^{47}Calcium in patients with rheumato d arthritis and osteopeni
Acta rheum scand. 15 145 1969 Togethe with B Olhagen and P R Izenstein

I the f llow ng these papers will be referred to by Roman umbers I–VI
Som additional results are also presented.

CONTENTS

INTRODUCTION

The dynamics of calcium retention in man — lunically the most important parameter f calcium metabolism — is incompletely known This holds true for normal conditions and al so for diseases which are frequently attended with disturbances in calc um metabolism and osteopenia, e g endocrine and gastrointestinal diseases

Most f our knowledge about the body s ability to retain calcium has been acquired by means of the classical" method fo meta bolic studies in which the d fference between th dministered and the excreted amounts of a substance, in thi case calcium is measur ed The technique f such balance studies has been known fo more than 40 years (2, 13, 52) The method has yielded valuable information especially in comparative studies f alcium retentio m patients and in healthy subjects The sources f orro f the method, although known at an early stage (107) became striking ly obvious, especially when the metabolic bal ance technique was used in measuring absolute instead f relative values Isaksson and Sjö-gren and others (62–67 128) drew attention to the low preci ion f the method and thus the lim tation of its usefulness Administration f non-absorbable trace substances (54 100 110 129) helped to improve the method but made it even more laborious

F r some years past the metabolic balance technique has made use of radioactive isotopes first strontium and then various calcium isotopes (9–11 reviewed 12, 20 23, 24 26 40 56 117 127 128) In this way som f the routes f excretion of calcium have been studied losely The endogenous calcium losses via the faeces in particular were thus studied (25 34 35, 40 58 59 112) These improvements of the technique have made t possibl to estimate calcium absorption from the intestine but they hav had less influence on the possibilities to measure the total retention of administered cal ium

As the systemati rrors connected with measurements f calcium losses in all the routes f xcretion can hardly be vercome the best technical solution must be d r t measurement f calcium retention The only known procedure fo this purpose is to admin ist radioactive isotope and to measure the retention by whole-body counting (15 16 28 29 42 105 106 108 121) The first experiments f this kind using rally administered ^{47}Ca were published in 1962 by Bob et al (21) and North et al (99) In 1964 when I began to study cal ium retention measured by whole-body counting after oral administration f ^{47}Ca (115 116) no other systematic studies had been published Later on, results were published of

studies of whole-body retention [of] ^{47}Ca in gastrointestinal diseases (36 37) and in patients with total gastrectomy (47) and primary biliary ci rhosis and sprue (1 70) The results were discussed as a measure of calcium absorption

The main purpose of the present study was to work out a method for measuring whole-body retention of orally administered ^{47}Ca and to investigate its clinical usefulness in healthy subjects and in groups of patients with certain endocrine and gastrointestinal diseases with and without osteopenia

Healthy subjects and patients were all given a ery small amount f ^{47}Ca orally varying from 1 3 μC The isotope was given after fasting overnight and four hours before the next meal was due. The isotope was mixed with a carrie of $CaCl_2$ (after desiccation) which equals 135 mg of ^{40}Ca dissolved in 30-50 ml of distilled water Immediately before th administration of the isotope background measurement was made by whole-body count ing The measurements were repeated after on hour and three hours and after 7 10 and 14 days The results t the last three count ings as percentage f the given dose – determined as the highest of the 1-hour or 3-hour values minus background – was designated as whole-body retention Thus when the figures f ^{47}Ca retention are expressed in per cent of given dose, this will always mean the percentage of initial whole-body radioactivity In all but the earliest studies the 2-week value was used as the standardized value for whole-body retention Systematic errors and results of duplicate determinations were described in Paper I All the patients except those after gastrectomy (Paper II) and those with rheuma toid arthritis and osteopenia (Pape VI) had their rdinary hospital or hom diet There was only a slight reduction in the range of the values for calcium retention when the healthy subjects had a standardized diet of 700-800 mg f calcium daily compared to their ordinary diet (Paper I)

Table I summarizes the mean values obtained for the whole-body retention of ^{47}Ca one and two weeks after ral administration f the isotope

Tabl I Whole-body retention of ^{47}Ca in per cent of given dose in healthy persons and patients

Groups of subjects	No of subjects	Retention % of gi en dose						
		at 7 days		at 14 days		diff rence		
		mean	SD	mean	SD	mean	SD	n
Healthy subjects	27	35 7	7 6	29 3	7 4	5 4	2 4	24
Status post gastrectomy	9	49 7	4 1	44 4	3 3	9 9	5 4	5
Regional enteriti with partial resection f small intestine	11	16 9	(n 8)	14 5	1 7	3 6	2 1	8
Pancreatic insufficiency	12	28 5	(n 10)	26 3	2 3	6 3	5 5	10
Primary hyperparathyroidism	9	52 4	12 2	39 6	10 6	12 1	5 2	8
Acromegaly	12	50 1	10 9	39 7	7 2	11 9	6 4	10
Rheumatoid arthriti with osteopenia	8	24 5	6 1	21 1	6 3	0 0	3 1	6
Cushing syndrom	9	33 7	6 3	24 4	8 5	7 9	2 9	8
Postmenopausal osteoporosi	7	34 5	5 3	26 6	3 8	7 9	3 8	7

Table II Whole-body retention and urinary excretion of ^{47}Ca in per cent of given dose in nine patients with Cushing s syndrome

Patients			At 7 days		At 14 days	
no	sex	age (y)	retention (%)	cumulative urinary excretion (%)	retention (%)	cumulative urinary excretion (%)
1	F	17	45 7	8 7	41 8	11 4
2	F	74	40 4	16 2	31 7	22 3
3	F	57	30 8	6 6	27 4	10 6
4	F	50	33 0	8 9	24 5	14 0
5*	F	41	33 5	3 9	22 7	6 4
6*	F	34	30 6	14 6	22 7	19 4
	F	33	27 4	13 2	19 3	–
8*	F	35	27 9	7 0	16 6	10 0
9	M	30		14 0	13 3	16 9
	Mean ± SD		33 7 ± 6 3	10 3 ± 4 1	24 4 ± 8 6	14 1 ± 5 5

* Carrier dose 90 mg of stable calcium instead f the standard dose of 135 mg

Som of the results ha been reported earlier

- in 27 healthy subje ts (*Paper I*);
- in ine patients after gastrectomy (Paper II) The retention of ^{47}Ca was found to be significantly increased It was suggested that these patients had increased absorption of calcium from the gut,
- in 23 patients with int stinal malab sorption of whom 11 had re gional enteritis and status post intestinal resection and 12 patients with severe pan reatic insufficie cy (Paper III) The former group showed a significantly lowered retention of ^{47}Ca, while the retention was within normal limits in the latter group
- in nine patients with primary hyp r p rathy oidism (Paper IV) The mean retention value was highe than in the healthy controls and the uri nary loss of ^{47}Ca was also increased These findings were interpreted as demonstrating an increased cal ium absorption from the gut;
- in 12 patients with a romeg ly (Paper V) The retention f ^{47}Ca was in reased, as was the urinary loss of both ^{47}Ca and stabl calcium The data were considered to show increased calcium absorption from the intestine;
- in eight patients with heumat id a th itis and teopenia (Paper VI) The whole group f patients showed a lowered value fo ^{47}Ca retention

A further two patient groups were examined late on namely patients with Cushing s syndrome and patients with post menopausal steoporosis

In nine patients with typical Cushing s syndrome and characteristic laboratory findings the mean retention of ^{47}Ca after seven days was almost identical with the corresponding value in the control group (Table II) After two weeks the mean value was somewhat lower than that of the controls but not significantly so

Tabl III presents the results obtained in seven patients with postmeno pausal o t oporosis In all of them repeated values for calcium in blood and urine, and inorganic phosphate in blood as well as alkaline phosphatases were normal The mean value for calcium retention did not differ from normal after seven and 14 days

Tabl III ^{47}Ca retention in per cent f given dose in seven women with postmenopausal osteoporosis

Patients		Retention	
no	age (y)	at 7 days (%)	at 14 days (%)
1	81	41 4	32 8
2	67	39 0	31 0
3	55	31 0	27 0
4	63	30 6	24 4
5	61	40 1	24 3
6	63	29 6	24 2
7	55	28 8	22 8
Mean ± SD		34 5 ± 5 3	26 6 ± 3 6

Total ndogenous lo ses of ^{47}Ca Table I shows the difference between ^{47}Ca retention in one week and in two weeks in all groups of examined subjects It can be considered a priori that this difference corresponds to the endogenous losses of ^{47}Ca in the second week, provided that all the absorbed calcium isotope had left the intestinal canal before the measurement on the seventh day Kinney et al (71) showed that this was the case in 87 % of their subjects and after ten days in all their patients In the three present patient groups the differenc in this respect was higher than in healthy subjects namely in those with primary hyperparathyroidism in those with acromegaly and in the hyperparathyroidism group

If we know the whole-body losses for a certain period, here the diff rence in two whole-body counting before and after the second week, as well as the urinary losses of radioactive and stable calcium we can estimate the total loss of stable calcium The specific activity of the calcium isotope must be assumed to be the same for all excretion routes at the same time

The above mentioned difference between the retention values at 7 and at 14 days afte administration of ^{47}Ca corresponds to the total loss of radioacti e calcium ($T_{47_{Ca}}$) The urinary loss of ^{47}Ca over this period is measured (Pape I) and can be designated as $U_{47_{Ca}}$ The urinary loss of stable calcium over the same period can be designated as $U_{40_{Ca}}$ From these data we obtain

$$\frac{T_{40_{Ca}}}{U_{40_{Ca}}} \quad \frac{T_{47_{Ca}}}{U_{47_{Ca}}} \quad \text{then}$$

$$T_{40_{Ca}} \quad U_{40_{Ca}} \quad \frac{T_{47_{Ca}}}{U_{47_{Ca}}}$$

where $T_{40_{Ca}}$ is the total loss of stable calcium in 24 hours between day 7 and day 14

This calculation is exemplified in Table IV by data from some of the patients in the acromegaly group (Paper IV) The total calcium loss in 24 hours for the whole group was about 1 5 g (Table IV)

The average total daily loss of radioactive calcium by the acromegalic patients for the period between day 7 and day 10 was 1 5 %, and for days 10-14 it was 1 2% The average daily urinary losses of ^{47}Ca during the same periods were 0 55 and 0 42, respectively These data indicate that the losses of non absorbed ^{47}Ca during the first part of the second week after ^{4} Ca administration were negligible already during the first part of the second week for the whole group

The urinary excretion of radio activity over the 14-day measuring period in patients with different diseases varied between 0 4 and 22 6 % of the given dose, when the amount of carrier was 135 mg The lowest value was recorded in a patient with mal absorption syndrome after intestinal resection and the highest value in a patient with hypogonadism and marked hypercalciuria (Table V) There was a high correlation (r 0 958 $p < 0.001$) between the cumulative excretion of the first three and the first 14 days respectively after administration of isotope (Fig 1) The quotient f these excretion val ues was 0 53 It will be seen from Figure 1 that the correlation between 3-day and 14-day cumulative ^{47}Ca excretion was also high when the amount of carrier cal ium was increased to 675 mg

Administration of supplementa y calcium forms part of the treatment in many

Table IV Calculated total loss f calcium in 10 patients with acromegaly

Patients no	sex	age (y)	Retention of ^{47}Ca at 7 days (%)	Retention of ^{47}Ca at 14 days (%)	difference T_{47Ca}	Urinary excretion of ^{47}Ca at 7 days (%)	Urinary excretion of ^{47}Ca at 14 days (%)	difference U_{47Ca}	Urinary excretion of ^{40}Ca, mean value (mg/24 h) U_{40Ca}	T_{40Ca} (see text) (mg/24 h)
1	M	41	72 7	62 3	20 4	8 7	10 7	2 0	366	3733
2	M	54	55 6	45 4	10 1	16 6	25 7	9 1	353	392
3	M	47	51 3	43 4	7 9	7 1	10 5	3 4	362	841
4	F	64	45 3	38 2	7 1	6 3	7 6	1 3	174	950
5	M	33	59 7	37 9	21 8	5 9	7 3	1 4	255	3971
6	F	63	45 0	35 6	9 4	6 0	7 1	1 8	256	1276
7	F	25	40 2	35 5	4 7	11 7	13 8	2 1	357	799
8	M	57	44 9	33 0	11 9	13 7	19 0	5 3	557	1250
9	F	31	34 2	29 5	4 7	13 1	15 2	2 1	417	933
10	F	45	39 6	25 7	13 9	11 1	16 4	5 3	341	894
Mean ± SE			48 8 ± 3 6	37 ± 2 5	11 2 ± 1 8	10 0 ± 1 2	13 3 ± 2 5	3 4 ± 0 8	344 ± 37	1604 ± 376

Table V Cum lative excretion of ^{47}Ca in per cent f given dose Carrier dose 135 mg of ^{40}Ca

Patients				Urinary excretion (%)			Whole-body rotention after 14 days (% av given dose
no	sex	age (y)	diagnosis	day 1	days 1 3	days 1 14	
1	M	62	Regional enteritis	0 6	1 6	3 5	12 1
2	M	60	Regional enteritis	0 05	0 2	0 4	12 8
3	M	25	Regional enteritis	0 7	1 7	3 9	11 5
4	M	44	Regional enteritis	1 1	1 6	2 6	10 8
5	M	47	Pancreatic insufficiency	4 7	8 1	14 9	33 2
6	F	42	Pancreatic insufficiency	1 2	3 6	6 7	19 6
7	F	47	Pancreatic insufficiency	1 5	1 7	4 9	32 4
8	F	64	Acromegaly	2 4	4 2	7 4	39 8
9	M	42	Acromegaly	3 0	6 6	10 7	53 2
10	F	57	Primary hyperparathyroidism	3 4	5 6	10 4	20 9
11	M	55	Status post gastrectomy	0 4	0 6	1 9	26 2
12	M	70	Rheumatoid arthritis	0 6	1 0	3 9	18 9
13	M	52	Osteogenesis imperfecta*	1 2	2 1	5 0	30 3
14	M	35	Idiopathic hypercalcuria*	4 4	7 3	12 4	23 5
15	F	43	Hypercalcuria hypogonadism*	7 0	13 1	22 5	34 1
16	M	56	Osteoporosis*	1 1	3 3	5 2	23 7
17	F	59	Biliary cirrhosis*	2 5	5 8	12	12 6
			Mean ± SD	2 1 ± 1 9	4 1 ± 3 3	7 6 ± 5 7	26 3 ± 12 0

* These patients were not reported in previous papers

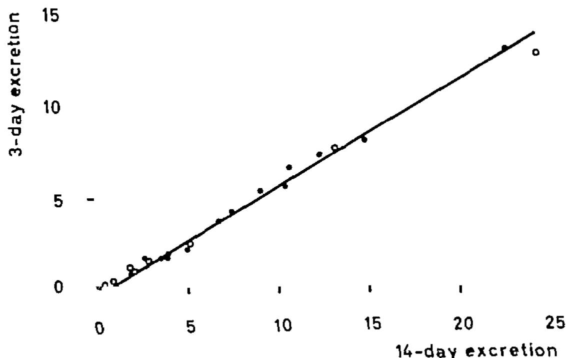


Figure 1 Correlation between cumulativ rinary excretio f ^{47}Ca (in % f given dose) ove the first three days and 14 days afte administration f the isotope ● epresents s tandard carri dose f 135 mg of $^{40}Ca^{++}$ and O epresents the highe carri dose f 675 mg

disorders of alc um metabolism Th ability to absorb and retain calc um in such disorders has not been made fully lear howev This study was therefore undertaken to investigate the ffect on ^{47}Ca retention f two diff rent carrie doses f stable calc um carri (135 mg and 675 mg) Th results are presented in T ble VI, which shows that there was a negative co relation between the carrie amount and th retention f alcium in pe cent f given dose The am observation fo calcium absorption has been made earl (36 46 90 reviewed 97 103,109 111) It will also be seen howeve that there was low-e threshold alue fo retenti n at about 8 10 % f th given dose none f the ubjects retained les than 6 % Higher amounts than 675 mg f calc um carri were not given It can be concluded that the retained amount f stable calcium was highe with the highe ar-rie dose This holds true even for the patients with malabsorption syndrome caused by region-al enteritis and intestinal esection

Table VI ^{47}Ca retention after 14 days in per cent of given dose in 17 patients Comparison f results obtained with a carrier dose of stable calcium f 135 mg and a carri r dose of 675 mg

Patients no	sex	age (y)	diagnosis	Retention of ^{47}Ca carrier dose 135 mg	675 mg	difference	Amount f carrier calcium retained (mg) carrier dose 135 mg	6 5 mg	difference
1	F	47	Status post gastrectomy	38 7	27 7	11 0	52 2	187 0	134 8
2	M	55	Status post gastrectomy	66 5	26 2	40 3	89 8	141 5	51 7
3	M	49	Regional enteritis	14 3	11 0	3 3	19 3	74 3	55 0
4	F	58	Regional enteritis	11 8	8 3	3 5	15 9	56 0	40 1
5	M	31	Pancreatic nsuffic ency	25 6	11 8	13 8	34 6	79 7	45 1
6	F	61	Pancreatic insufficiency	20 0	11 0	9 0	27 0	74 3	47 3
7	M	45	Pancreatic insuffic ency	23 1	15 0	8 1	31 2	101 3	70 1
8	M	55	Pancreatic nsuffic ency	28 3	8 8	19 5	38 2	59 4	21 2
9	M	47	Pancreatic insufficiency	33 2	19 5	13 7	44 8	131 6	86 8
10	F	42	Pancreatic insufficiency	19 6	13 5	6 1	26 5	91 1	64 6
11	M		Pancreatic insufficiency	42 1	18 9	23 2	66 8	127 6	0 8
12	M	59	Pancreatic insufficiency	28 8	18 4	10 4	36 2	110 7	74 5
13	F	25	Pancreatic insuffic ency	27 1	12 1	14 9	36 6	82 4	45 8
14	M	32	Pancreatic insufficiency	15 7	11 1	4 6	21 2	74 9	53 7
15	M	57	Duodenal ulcer*	23 0	16 2	6 8	31 0	109 4	78 4
16	M	31	Duodenal ulcer*	26 8	15 2	11 6	36 2	103 3	67 1
17	M	24	Vitamin D resistent osteomalacia	54 7	22 0	32 7	73 6	138 7	65 9
			Mean ± SD	29 3 ± 14 4	15 6 ± 5 7	13 6	39 4 ± 19 3	102 6 ± 34 5	63 1

* These patients ha o not been reported bef re

DISCUSSION

Th e concept f calcium etention

The present work deals with the concept f calcium retention which, in this context, means *the fraction f an rally administered dose of* calcium that i retained in the body This cal cium retention is the result of several functions Gastrointestinal absorption of calcium obvi ously plays a major role The retained por tion has evidently passed through the wall f the small intestine, and has been further dis tributed. What is then kept in the body depends on the balance between the avidity f the tis sues f cal ium and the excretion of calc um through the intestine, kidneys and skin.

Obviously the mathematical expres ion f the retention f rally administered calcium is the differenc between calc um absorbed by the gut and the losses of absorbed calcium For the clinician the important information is the fraction f total administered calcium that the patient retains after ingestion. Therefore, the present work has concentrated on this aspect.

Int t l abs pti n of al m

One of the main objects f studies f cal um metabolism in man is to ttain an estimation f the amounts f calcium in rdinary food that is absorbed and retained Such studies have shown that the retention f calcium from food is dependent on the ingredients of the food (reviewed 61 75 130) and also influenced by the capacity to digest and absorb the food constituents As was mentioned in the Intro- duction, it is extrem ly difficult to attain the necessary accuracy by lassical metabolic studies involving administration f a diet of *known and constant composition. Several tech-* niques claimed to measure calcium absorption hav been described (27 32 76 81 83 84 97 122)

Since the object of the present study was to arrive at a standardized test for measuring the retention of calcium after it had been ab- sorbed in the intestines it was decided to giv *radioactive calc um orally as an easily soluble* salt, cal ium chl ride, and with moderate amount f calcium carrier This amount of carrier is sufficient for the specific activity f the administered sotope to be designated as low Administration of isotope with low spe- cifi activity probably gives better discrimina tion than does administration f isotope with high specific activity

An interesting fact is that sev ral authors *have been able to demonstrate higher fractional* absorption f calcium afte administration f a low-calcium diet (60 77 78 88 89 97) Frac- tional cal ium absorption was laimed to be relatively lowe after substantial increase in *the administered amounts f calcium* (78 118) These results were obtained by means of classical metabolic studies r modifications thereof

In estimating the total amount f calcium absorbed and retained it is essential to take

into consideration the amount of stable calci um excreted into the intestine and mixed with the isotope and its carrier This calcium is partly secreted by the gastric and intestinal mucosa (53 114) the bile and the pancreatic juice The bile contains substantial amounts of lime salts (22 56) It is reasonable to assume that, because of the unknown amount of calcium mixed with the isotope during the test, it is im possible to calculate the amount of stable cal cium absorbed together with the isotope Few investigators seem to have considered such factors when evaluating calcium absorption (94)

For these and other reasons the retention of calcium as measured by the present method should not be directly held equal to the absorption of calcium

L o s s e s o f c a l c i u m In the kidney cal cium is treated as a threshold substance Excretion is thus partly proportional to the serum calcium level The tubular reabsorption is ef fectively stimulated by the parathyroid hormone (95 123)

As regards the other endogenous routes of elimination via the intestines the skin and breast milk, the regulating factors are less known The endogenous losses of calcium via the gut do not surely seem to vary with the plasma calcium (69) The endogenous loss of calcium via the faeces is however of such an order of magnitude as not to be neglected Thi re-excreted and lost part of absorbed calcium can almost equal the losses via the urine (40 97) Together with the losses of calcium through the skin which can be of the same order of magnitude as the the urinary losses of calcium (31 62 67 125) the endogenous faecal losses of calc um constitute a great source of error which is difficult to measure, and which attaches notably to determinations of retention carried out as classical metabolic studies

It is evident from this discussion that the urinary excretion of administered isotope does not with certainty comprise the greater part of the endogenous calcium losses

With the present method of measuring the ^{47}Ca retention the different routes of elimination of calcium from the body need not be taken into consideration This must be regarded as a great advantage particularly as mentioned earlier since great difficulty and uncertainty attach to the measurement in clinical routine work of endogenous faecal calcium and, the calcium losses through the skin

One way of estimating the whole body e endogenous losses of ^{47}Ca is to measure the difference between the 7-day and the 14-day retention If the non absorbed ^{47}Ca after sev en days can be designated as negligible the difference must equal the total endogenous loss It was shown in Papers IV and V that this endogenous loss was higher in such conditions as hyperparathyroidism and acromegaly than in the healthy subjects (Tab IV) The loss of ^{47}Ca and ^{40}Ca in the urine between day 7 and day 14 together with the decrease in the reten tion f ^{47}Ca can be used in calculating the total los of stable calcium (see Page 10)

R e t e n t i o n o f c a l c i u m As has already been mentioned, the retention of calcium can be regarded as a function of the intestinal absorption of calcium The whole-body retention is the difference between absorbed calcium and endogenous losses of calcium It cannot be estimated by direct measurement before the non absorbed portion of orally administered calcium has been liminated from the intes tinal tract. After this period of time we can obtain a value f r the whole-body retention

W thin on to three hours an orally admin-

isterod calcium isotope will have reached maximum concentration in plasma (6 18 69 79 95) The calcium isotope is rapidly transported from the plasma to the bones and other tissues

There is some uncertainty about the rder of magnitudo f the ability of the soft tissues to retain calcium There exist no measuring methods suitable f this purpose but a few such studies habe been made (29) The model f Bauer et al f cal ium uptake in the bones also hows the magnitude f exchangeable cal cium (12 40 127) According to Bane et al the calcium uptake in bone (accretion) would be about 0 5 g/24 h and the exchangeabl part of the skeletal mas 5 g of cal ium ion The rapidly exchangeable calcium fraction in the bones would thus comprise only about 1/200 f thei calcium content Some f these fig res ha been confirmed by e g Dymling 39 40) Heaney et al (55–57) and M lhaud et al (85) The re-transport f calc um to the blood stream from the bones i considered to occur via cells and by enzymatic hydrolysis (14 55 124)

In th present study it was found that the retained amount f stabl calcium in ariably increased when the amount f carrier was increased fr fold (Tab VI) Highe amounts of carrier were not used. The increase f retention varied between 21 mg and 135 mg f ^{40}Ca This may be an important considera tion in therapeutic trials with administration of large amounts f calcium rally W th the present method t can obviously be establ shed how much f an ral calcium dos will be retained afte certain period f tim though not late than within two to three weeks afte administration

As was mentioned in the Introduction, N rth et al and Boh et al in 1962 published results of whole–body measurements of ^{47}Ca retention North et al (99) in their six and Bohr et al (21) in their four patients used high amounts of calcium as a supplement to the patients diet North et al gave the isotope with about 100 mg f calcium as calcium chloride in water and Bohr et al ga it with a glass f milk The measured calcium retention was 10 2 16 5 % f the given dose after one week and 4 6–6 6 % after 10 days respectively Deller (36 37) by whole–body measurements in seven healthy women found in 1965 and 1966 retention values f 28–64 % of the given dose, when 200 mg as calcium lactate were given as stabl calc um carrier and f 20–32 %, when th arrie was given as 200 ml f milk Agnew (1) in a study f 19 healthy women found i 1969 a retention f 49 ± 6 5 %, when the carri was 10 mg f alc um hloride wate

Balche (16) emphasized in 1965 the problem of the geometrical measuring rro in whole–body measurements made with mmova ble solid rystals See lso Oliver and War ne (101)

The retention values in healthy subjects obtained in the present study around 30 % (see Results) are not directly comparabl with any of the values reported by the afore–said au thors as the technique used diff red on sev r al important points

Cli al appli at

Clas ic l metabolic studies are f limited val ue in routine diagno is and treatment f disturbances f alcium metabolism The method presented her f direct measurement f cal um retention will satisfy need in this respect Its ability to discriminate between dif

ferent conditions attended with disturbed calcium metabolism in a wide sense has been tried in various groups of such diseases

The malabsorption syndrome As discussed above the calcium retention test behaves differently in maldigestion malabsorption of the intestinal mucosa, and malnutrition In **maldigestion** i e insufficiency of the external pancreatic secretion, the patients retain normal amounts of calcium Since the total losses of calcium during the second week of this study does not seem to differ from the normal (Table 1) it is probable that the normal retention found in most of these patients (Paper III) also implies normal absorption This is in accordance with the finding in pancreatic insufficiency of a normal or possibly hypertrophic (73) intestinal mucosa

This normal retention f radioactive calcium does not necessarily mean that the utilization f calcium from the food is normal (Paper III) Furthermore it gives no clue to the amount of endogenous stable calcium that, especially in instances with oluminous stools, may be lost, bound to protein and to fatty acids Osteopenia is less frequently observed in such patients than in patients with 'pure malabsorption (see below Paper III 45) The significance of vitamin-D deficiency in these patients in connection with steatorrhoea is poorly known (7 35 41 90)

In the group with **malabsorption** due to regional enteritis and partial removal of the small intestine the retention value after two weeks was low The urinary loss of stabl calcium was also low These findings indicate low calcium absorption, i e a condition f pure malabsorption (33 68) Endogenous losses of calcium in faeces and perspiration could not be estimated until non-absorbed isotope had passed through the intestine The loss of whole-body activity during the second week of the studies did not exceed the normal average when calculated as a percentage of the given dose On the other hand, in relation to their retained whole-body activity the patients with regional enteritis showed higher losses than the normals Protein losses from the intestine have also been reported to occur in this disorder If the endogenous calcium losses via the intestinal canal had really been great in the patient group a greatly increased endogenous elimination of ^{47}Ca could have been expected in the last week of measurements It thus seems probable that the low oral ^{47}Ca retention corresponds to a low absorptive capacity of the gut for calcium It can not be excluded, however that some patients had somewhat increased endogenous faecal losses (Paper III)

The present method can therefore be used in establishing whether the condition is one of pure malabsorption or of maldigestion This is illustrated by the patients with regional enteritis after intestinal resection (Paper III) and by the gastrectomized patients (Paper II) respectiv ly

Malnutrition is common in gastrectomized patients partly because of maldigestion (81) The calcium retention was strikingly high in our patients (Paper II) In addition, the difference in retained amount after one and two weeks respectively was small This indicates that in malnutrition there is high whole-body retention with low endogenous total loss of calcium These patients unlik those with 'pure malabsorption, were evidently able to utilize calcium as an easily soluble salt under fasting conditions The role of the intestine trans t time is uncertain (80)

The cause of the increased calcium reten tion in gastrectomized patients with maldiges tion and malnutrition is obscure Nicolaysen demonstrated that in calcium deficiency states of animals there is increased retention of dietary calcium (88) Malm (77) showed that healthy dults n low-calcium diet could increase their calcium retention i e adapt themselves to a calcium deficiency state Nordin et al (92) and Haas et al (49 50) sed in fusion of stable calcium to establish increased retention also f parenterally administered calcium in deficiency states So there are data indicating that states of malnutrition with respect to calc um can be marked by an increased utilization of administered calcium The method used in the present study also yielded raised alues for retention i such cases

Up to now nly on factor the parathy roid hormo e has been recognized as being involved in the causation f increased calcium absorption in calcium deficiency states The current view is physi logically that the hormone is released by on stimulus only hypocalcaemia This is presumed to be th back ground f the linical condition f secondary hyperparathyroidism (43 44 51 82, 104 119 reviewed in 72 148) Such an inc ease in para thyroid function, secondary to calcium defi c ency might increase the absorption f cal ium from the gut, when intestinal function is intact Secondary hyperparathyroid sm has also been demonstrated in pure malabsorption states (4 93, 94) and aft gastrectomy (48)

Se da y hyp p athy idism can be established with certai ty only in pa- t ents with low serum calcium levels In addi tion the increased concentration f parathyro d hormone leads to losses f phosphate with resulting hypophosphataemia and hyperphosphaturia as w ll as to a rise in alkaline phos phatases of skeletal rigin in the blood In the absence of any of these criteria, notably hypocalcaemia — which is in fact, s ldom demonstrated in these conditions — secondary hype parathyroidism cannot be established, as long as a practically usabl method for analysis of parathyroid hormone in serum is not available In the group of patients with the malabsorption syndrome that was examined by the ^{47}Ca retention method described here secondary hyperparathyroidism was demonstrated n higher frequency only in those who had regional enteritis and undergone intestinal resection All the patients with secondary hyperparathyroidism had probably co-existing osteomala cia (Paper III)

It has been as rted that secondary hyper parathyroidism can occ r in the presence of seemingly normal serum calcium levels The c use of the hyperparathyro dism would be acute or hronic calcium deficiency Secondary hyperparathyro dism (with inc eased bon resorption) has been reported to occ r in many animal species (72 113) Increased parathyroid activity in the blood would occu without co-existing osteomalacia Administration f cal ium would then reduce this secondary overactivity f the parathyroids This has recently been shown by means of advanced isotope stud ies and conf rmed by bone biopsies (9 30 10? 118) Gastrectomized patients ha e probably secondarily increased concentration of para thyroid hormone in their blood (48) It is thus probable that the parathyroid hormone could be one of the factors that promote the utiliza tion of administered calcium when intestinal function is fai ly well preserved

P ima y hyperparathyroidism In patients with primary hyperparathyroidism

high retention of calcium could be demonstrated one and two weeks after oral administration of the isotope (Paper IV) The loss f stable calcium and isotope calcium in the urine was also increased. The total endogenous loss of calcium expressed as the difference between the retention value in the first and in the second week, was high Together these observations support the presumption of a raised calcium absorption in primary hyperparathyroidism It has earlier been suggested that the parathyroid hormone would stimulate the absorption f calcium from the gut (120 reviewed 5 19 26) (Paper IV) In the present study this effect seemed to be strikingly noticeable In view f the fact that the retention of ^{47}Ca was increased in the group of patients with primarily raised levels of parathyroid hormone in the blood, it seems more probable that a secondary increase of parathyroid hormone in the blood would be at least one of the factors contributing to the high retention value in the gastrectomized patients (Paper II)

A c r o m e g a l y The effect on calcium retention of a raised level of growth hormone in the blood was studied in a group of acromegalic patients Whole-body retention was high, as were the total endogenous calcium losses These were estimated from the decrease in whole-body retention during the second week of the measuring period. The excretion f the isotope in urine also seemed to be increased The sum of the retention and endogenous losses ndicates high intestinal absorption of calcium in acromegaly The aetiology of increased intestinal calcium absorption in acromegaly is unknown The increased absorption may possibly be related to the high body weight, great bone mass and large intestinal canal None f these factors however would alone be sufficient to explain the high retention in this group of patients (Paper V 17 87) The increment of calcium retention measured by means of classical metabolic balance studies after growth hormone administration is still a matter of dispute (3, 28) High accretion values have been described in acromegalic patients (17 85 87) In spite of hypercalciuria and high endogenous losses none of our patients showed osteopenia All this indicates that growth hormone may increase utilization of orally administered calcium (Paper V 35)

C u s h i n g s s y n d r o m e is characterized by high endogenous cortisol production In many of these patients the condition is complicated by osteopenia, which has the greatest resemblance to rapidly progressing osteoporosis This is also the most dreaded complication in the treatment of patients with corticoids in pharmacological doses (2 126) Calcium absorption from the intestine has been reported to be low or normal (8 18, 86 95 126)

Nine patients with Cushing s syndrome were examined for retention of ^{47}Ca (Table IV) The excretion of isotope in the urine could also be measured in som of them The calcium retention for the group was within the normal range The difference between whole-body retention after one and after two weeks was higher but not significantly so Isotope excretion with the urine was strikingly high These results indicate increased endogenous losses (74) of calcium in the presence of a probably normal calc um absorption from the gut Earlier findings f impaired calcium absorption in subjects with high concentrations of corticoids in blood could thus not be verified in this study

The result of the present work indicates that the calcium deficiency in patients with

high cortisol levels in the blood would rather be caused by increased endogenous losses of calcium and possibly to increased bone resorption (8 86 126) Th re was evidence for normal absorption from the gut when the isotope with carrier was given under fasting con ditions

Rh m toid arthritis with os teope ia Osteopenia is common complica tion in rheum toid arthritis Th ause of the osteopenia is unknown the discussion on this subject in the literature is reviewed in Paper VI All the patients examined had osteopenia, and were treated with salicylic acids and three had sm ll amounts of cortisone They showed decreased retention of calcium both after ne and after two weeks The amount f stabl cal cium in urine was not markedly increased (ex retion of isotope in urine was not measured) The total endogenou elimination of calc um meas red as the diff rence between retention after one week and afte two weeks was rathe low These observations suggest that the absorption f calc um from the gut was probably decreased in these patients It i f course possible that the salicylic acids and the small cortisone doses can hav played a part in this espect

Frost et l by examination f biopsy specimens from ibs found evidence f steopeni in patients with rheumatoid arthritis who had had no treatment fo years Heaney demon strated increased affinity fo calcium around and in affected joints (see references in Pape VI) It i therefore readily presumed that in rheumato d arthriti central parts f the skel eton, such as the ertebrae, receive too littl calc um in the competition fo the limited supply f calcium from the intestine Immobi lization would probably also play a part in the aetiology of osteopenia in rheumatoid arthritis

Postme opausal osteop r sis Six patients with postmenopausal osteoporosis were examined in the present study In one of them immobilization f r fou months had caused disabling osteopenia All of them had a normal retenti of orally administered ^{47}Ca and a normal urinary excretion of radiocalcium

Earlier studie have reported onflicting results regarding intestinal calcium absorption, skeletal accretion, and sk letal resorption in postmenopausal osteoporosis The in testinal absorption f calcium has been report ed to be normal (69) low (83, 84) Dymling, in kinetic studies found a probably normal accretio rate of calc um (40) whe eas other investigators have reported decreased figures (83, 84) Som authors have reported an in eased skeletal resorption, but others hav found normal alues (85)

The present study i a small numbe f patients indicates that whole-body retention and intestinal absorption f rally administ red calc um chloride in a fasting condition may be normal in postmenopausal osteoporosis

The l al e f the method

One advantage f the present method is that it allows di t measurement of the whole-body retention of administered calcium The diffic lties attaching to the collection of ex cretory products and measurements f cal ium in these are thus avoided Anothe advantage is that small amounts of isotope are required The earlier methods which were combined with metabolic studies required

much greater amounts of radioactivity by mouth (26 34) Small amounts of isotope can be used because of the high sensitivity f the whole-body counter which in turn is due to markedly reduced background activity With the use of small amounts of isotop with short half life the measurements can b repeated virtually an unlimited number of times As an example may be mentioned the repeated determinations of whole-body retention in the malabsorption patients in the present study Naturally the value of a low-activity method in itself is that the patients will receive a minimal amount of isotope In the present studies quantities of isotope as low as 1 0 µC were used With this amount of isotope however alcium retention cannot be measured for longer than two or in occasional cases three weeks

The clinical usefulness of the method is obvious in pathological conditions that invol e the ntestinal tract The method thus discrim mates between conditions of pure malabsorptions and of pure maldigestion (Paper III) W th administration f food simultaneously w th the isotope further discrimination of the different forms f the malabsorption syndrome will probably be possible (Paper III) Administration f a higher carrier dose will very likely increase the possibilities f differential diagnosis By repeated determ nations with high carrier doses it w ll probably also become pos ible to obtain information on the amount of calcium that the patient can absorb and retain

The method also perm ts study of the nature and degree f hormonal influenc on alcium metabolism This applies for instance to states f over-production f parathyroid hormone and cortisol, which are ften compli cated by osteopenia It is therefore important to determine the ability to retain calcium of some f these patients This holds true also f r other forms of endocrine and non-endocrine osteopenia in which several causal factors probably contribute to the loss f skeletal mass With the above mentioned developments of the technique using repeat ed measurements of retention and administra tion of higher carrier doses the method will probably be still more reliable in detecting defects in the ability to retain calcium in these patients

A technique for measuring the patient s to tal loss of stable calcium was described under Method and Results It involved measurement of the difference of whole-body retention of ^{47}Ca before and aft r the second week of the study It also required data on the daily exc e-tion of stable and isotopic calcium in the urine during this period. To ensure accuracy in each individual study the last period should be started on the 10th day after ingestion of the isotope when all non-absorbed ^{47}Ca would be lost The study should also be extended over a few days more than two weeks with frequent whole-body countings during thi period It is suggested that when combined with a clas sical metabolic tudy this procedure would allow calculation of the losses via different excretion routes

Several studies on the endogenous losses of calcium from the body hav earlier been made with intravenously injected isotope f high specific activity (see Introduction) In the present studies the isotope is accompanied by a stable calc um carrier dose and is thus of a low specific activ ty when it reaches the blood The isotope given orally in that manner generally reaches its maximum activity in the blood 1 3 hours after ingestion We have therefore started trials with nfusions f ^{47}Ca

of low specific activity During two hours a stable calcium carrier f approximatively the absorbed amount, determined from the previous study with oral isotope is given together with ^{47}Ca The whole-body retention of this activity compared to the previous ral ^{47}Ca retention study would yi ld a fair meas re of the absorbed amount of calcium So far we have used this technique in only a few patients Future studies are required to establish whether this low specific acti ity infusion will mean any decisive improvement compared with earli r techniques

In the present study there was considerable overlapping of the retention values between some disease groups and between disease and control groups This may of course be referable to inability of the method to disc iminate clearly between a healthy and a ick person, and between one metabolic disturbance f calc um and another W th continued work to improve the technique these short-comings may be remedied It is equally probable however that what might her be designated as disadvantages of the method would, in fact, indicate that the different disease group have much in common from a mechanistic iewpoint and that our knowledge concerning those problems s imperfect

SUMMARY

A method for measuring calcium retention of a single oral dose ^{47}Ca is described. A whole-body counter was used for the estimation of this retention.

The main advantages of the technique are that it allows direct measurement of the retention without collection of urine, faeces and sweat, that it involves the administration of extremely small doses of an isotope with a short half life and therefore allows repeated measurements at short intervals, that it can be used also on ambulatory subjects, and that it causes very little discomfort to the patient.

The error due to geometrical and biological variations was 1.7% of given dose. In 27 healthy subjects the retention of ^{47}Ca one week after the administration was 35.7±7.6% and after two weeks 29.3±7.4% of the given dose.

The ^{47}Ca retention was measured in groups of subjects with disorders in which disturbances in calcium metabolism with or without visible osteopenia are more or less common, such as malabsorption, maldigestion, malnutrition after gastrectomy, acromegaly, primary hyperparathyroidism, Cushing's syndrome, rheumatoid arthritis, and postmenopausal osteoporosis. Calcium retention was decreased in patients with regional enteritis and in the rheumatoid patients, and was increased in the postgastrectomy state, in acromegaly, and in primary hyperparathyroidism. In the remaining groups the retention was within normal limits.

A method is suggested for calculation of the total losses of endogenous calcium, based on the values for calcium retention at 7 and 14 days and the urinary losses of calcium.

The therapeutic value of high doses of calcium salts was evaluated by increasing the carrier dose of stable calcium from 135 mg to 675 mg. The amount of retained stable calcium increased in all the subjects, even in those with malabsorption after intestinal resection for regional enteritis.

Further developments of the technique for measuring calcium retention are suggested, including a combination of the whole-body-counting technique and a modification of the classical metabolic studies, and studies of the elimination of calcium from the body after intravenous infusion of ^{47}Ca.

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Supplementum 510

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LEFT HEART FAILURE IN ACUTE MYOCARDIAL INFARCTION

A Clinical Haemodynamic and Therapeutic Study

by

ANDREAS SJÖGREN

STOCKHOLM 1970

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PREFACE

The introduction of specialized units for the care of patients with acute myocardial infarction has led to a clear reduction in hospital mortality. In 1967 a coronary care unit was introduced at Serafimerlasarettet in Stockholm and this resulted in a fall in mortality when compared to that in patients simultaneously admitted to the general wards. A further reduction in hospital mortality of myocardial infarction will depend on improved management of various complications including that of heart failure.

A study was therefore started at the beginning of 1968 in the coronary care unit at Serafimerlasarettet dealing with clinical, haemodynamic and therapeutic aspects of left heart failure in the early stages of acute myocardial infarction. With the publication of the findings I would like to express my gratitude to all who gave assistance while the study was under progress.

To Professor Gunnar Biörck, Head of Department of Medicine, Karolinska Institutet at Serafimerlasarettet, I am greatly indebted for advice and support as well as placing the necessary facilities at my disposal. Erik Orinius, M.D. assisted in the planning and continously followed the study as well as reviewing the manuscripts. Torbjörn Lundman, M.D. introduced me to computer analysis. Fredrik Wahlberg, M.D. read the manuscripts.

Professor Bengt Pernow placed the facilities of the Clinical Physiological Laboratory at Serafimerlasarettet at my disposal and reviewed the manuscripts. I thank him and his collaborators including Erik Berglund, M.D. and Dr. Lennart Jorfeldt for their help.

My thanks are also due to Alf Holmgren, M.D. who tested the resonant frequency of the catheters used, as well as Bengt Jonsson, M.D. and Harald Eliasch, M.D. for valuable discussions of different aspects of this study.

Dr. David Jewitt, introduced me to the technique of flow guided catheterization. Gunnar Törnell, M.D. and Dr. Göran Skogsberg generously agreed to review the chest X-ray films. Dr. Graham McCarthy gave linguistic help. Most autopsies were performed by Dr. Hans Nordenstam.

Much gratitud falls on the nurses of the coronary care unit who under the guidance of Miss Ulla Lindgren have greatly contributed to the effective running of the unit. Miss Gunvor Jepson ably assisted with the catheterizations.

Miss Eva Candal helped with the illustrations, and Mrs. Ingrid Braunstein, Miss Lisbeth Gyllenstierna, Mrs. Gunilla Haag, Mrs. V eca Hultén and Miss Rhode Jansson typed the manuscript. Mrs. Kim Hellman helped with the bibliography.

Mr. Staffan Ekblom gave valuable ad ice on statistical problems through the generous help of Astra Co.

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CONTENTS

The last decade has seen important advances in the management of patients with acute myocardial infarction. In several centers corony care units (CCU) have been established and the benefits of intensive supervision and early treatment of complications has led to a reduction in hospital mortality (Killip & Kimball 1967 Lawrie et al. 1967 Lown et al. 1967 MacMillan et al. 1967 Restieaux et al. 1967 Wallace et al. 1967 Meltzer 1968, Sloman et al. 1968, Thomas et al. 1968 Björck et al. 1969 Hofvendahl et al. 1969 and Isacsson et al. 1969)

This reduction in mortality has resulted primarily from the successful management and prevention of cardiac arrhythmias In contrast the results of treating heart failure after infarction have been disappointing (Meltzer 1968) Heart failure has been noted in 30 to 70 per cent of patients with acute myocardial infarction (Julian et al. 1964, Lown et al 1967 Restieaux et al 1967 Bergqvist et al. 1968 Meltzer 1968 and Thomas et al 1968) In the majority of patients it occurs transiently and is manifest clinically by dyspnoea, a third heart sound and pulmonary rales. Some patients deteriorate further and show the classical picture of fulminating pulmonary oedema. A number of authors have noted that the prognosis of patients with left heart failure is worse than in those without failure (Rosenbaum & Levine 1941 Honey & Truelove 1957 Peel et al. 1962, Hughes et al. 1963 Meltzer 1968 and Norris et al. 1968)

Because the successful management of arrhythmias in acute myocardial infarction has been mainly due to their early detection and treatment it seems worth exploring a similar approach in patients with heart failure. I the present study an attempt has therefore been made to identify the early stages of heart failure in patients with infarction utilizing simple clinical methods. The importance of individual clinical signs and symptoms have been evaluated and correlated with simultaneous haemodynamic studies Subsequently patients with early heart failure as judged by haemodynamic criteria, have been treated with a cardiac glycoside and a diuretic. This part of the study involves a comparison of the acute haemodynamic effects of the cardiac glycoside ouabain, and the diuretic frusemide (Lasix®)

The haemodynamic changes n patients with acute myocardial infarction have been increasingly investigated since the early 1950 s (Pritchard & Hellerstein 1950 Gilbert et al. 1951 Freis et al. 1952, Gilbert et al. 1954, Smith et al. 1954 Gammill et al 1955 Gunton et al. 1957 Lee 1957 Broch et al. 1959 Murphy et al. 1963, MacKenzie et al. 1964, Malmcrona & Varnauskas 1964 Thomas et al. 1965 a, Thomas et al. 1966, Nager et al. 1967 Shillingford et al. 1967 and Ramo et al 1969) Several authors have noted a clear association between a low cardiac output, clinical severity and poor ultimate prognosis.

More recently flow guided catheterization of the pulmonary artery has been introduced as a bedside procedure in severely ill patients (Dotter & Straube 1962 and Bradley 1964) and it has also been used patients with acute myocardial infarction (Valentine et al 1966, Fluck et al. 1967 Pain et al. 1967 Balcon et al. 1968 and Stannard et al 1968) Employing this method, the pulmonary artery pressure may be recorded continously at the bedside Since the pulmonary artery diastolic pressure is closely related to left ventricular filling pressures (Kaltman et al. 1966 and Jonsson & Sanai 1970) it has been used in this study to indicate early left entricular failure. An additional advantage of a catheter in the pulmonary artery is that it allows central Indocyanine green dye injections to be made, so providing more reliable dye dilution

curves in patients with low cardiac outputs and slow circulations (Oriol & McGregor 1967)

In most centers cardiac glycosides and diuretics are used to treat left heart failure in patients with acute myocardial infarction. However the beneficial effects of cardiac glycosides have not been established and uncertainty has persisted since this therapy was first advocated by Herrick in 1912 in his classical paper The negative chronotropic effect is not questioned (Willems & Schüller 1959) but whether a positive inotropic effect is produced by digitalis is uncertain. Recent haemodynamic studies in patients with acute myocardial infarction have not clarified this problem since the patients investigated were not in marked left ventricular failure (Malmcrona et al. 1966 and Balcon et al. 1968)

The question is important since cardiac glycosides may predispose to the development of serious cardiac arrhythmias when given in acute infarction (Hood et al. 1967) In the present study therefore the acute haemodynamic effects of a short acting cardiac glycoside, ouabain, have been followed in patients with heart failure as suggested by an elevated pulmonary artery diastolic pressure. In addition, because the cardiovascular effects of the potent newer diuretics have not been studied in acute myocardial infarction, the haemodynamic changes which follow intravenous frusemide have been measured and compared with those after ouabain in a cross over trial.

The present work has been divided into three parts.

Part I The scope of the problem is defined in a study of the incidence, clinical characteristics and prognostic importance of left heart failure in a large consecutive series of patients admitted to the CCU of Serafimerlasarettet in Stockholm.

Part II The haemodynamic changes in 50 patients with acute myocardial infarction are presented with special reference to the pulmonary artery diastolic pressure and its relationship to clinical and laboratory findings.

Part III The early haemodynamic effects of ouabain and frusemide (Lasix®) are compared in patients with raised pulmonary artery diastolic pressures.

PART I

A CLINICAL STUDY OF LEFT HEART FAILURE IN 363 CONSECUTIVE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION TREATED IN A CORONARY CARE UNIT

With improved results in the management of complicating arrhythmias in acute myocardial infarction the mortality in heart failure will gain importance. It is well recognised that the prognosis of patients in heart failure after an infarction is reduced (Master et al. 1937 Mintz & Katz 1947 Rosenbaum & Levine 1941 Honey & Truelove 1957 Peel et al. 1962, H ghes et al. 1963 Meltzer 1968, and Norris et al 1968) On the other hand, little attention has been paid to elucidate which patients develop heart failure in acute myocardial infarction, nor has attention been paid to this finding in relation to the past history as regards heart failure.

The purpose of this part of the present investigation was therefore to determine the incidence of left heart failure in patients with acute myocardial infarction as well as to study its characteristics and prognostic significance in a CCU The study was performed on a consecutive series of patients admitted to the CCU of Serafimerlasarettet in Stockholm January 1 1968 to September 14 1969

MATERIAL AND METHODS

Admission policy and criteria

Serafimerlasarettet, which is a teaching hospital, serves an undefined population within greater Stockholm and has 200 beds for general medicine. Acute admissions are received in the Casualty Department. With the introduction of the CCU the staff of the Casualty Department were instructed to contact the CCU immediately following the admission of a patient who after a rapid and preliminary appraisal might fulfill at least one of the following *admission criteria*

1. central chest pain lasting for more than 15 minutes beginning within the last 48 hours
2. frank pulmonary oedema without previously known valvular lesion
3. shock without suspicion of acute hypovolaemia or intoxication
4. syncope with electrocardiographic evidence of acute myocardial infarction.
5. intractable angina pectoris

The last two criteria were added on September 18, 1968

General care and organization of the CCU

The patients were originally treated in a temporary unit consisting of 3 single rooms (January 1 1968 until October 1 1968, with an intermission of the month of July) From October 11 1968 until September 14, 1969 the patients were treated in a 7 single room unit. During the earlier period, with the 3 bed unit, only about half of the patients fulf lli g the above criteria for admission could be received at the CCU The principle for selection was the availability of a bed in the CCU at the moment of call from the Casualty Department (Biörck et al. 1969) The duration of stay in the CCU was set according to defined criteria and terminated irrespective of time of day With the introduction of the 7 room unit, almost all patients fulfilling the admission criteria could be received

Both units were administered similarly The patients ECG were monitored on a bedside oscilloscope and on a slave oscilloscope placed centrally easily seen from the supervision area. The oscilloscopes were equipped with heart-rate meters giving acoustic as well as optical alarms, and automatically starting ECG registration on exceeding pre-set

limits. The rooms were equipped with a piped oxygen supply and mercury manometers on the walls. In the central supervision area there was a DC-defibrillator, transthoracic pacemaker catheters and battery operated pacemakers of "on demand" type. Transvenous pacemaker catheters were introduced under fluoroscopy and for this procedure the patients were taken to a laboratory outside the CCU.

The nursing staff was specially trained and had considerable freedom to administer drugs according to principles written in a detailed treatment programme. Their training included knowledge of electrocardiography with special emphasis on the interpretation of the arrhythmias. They were trained to defibrillate on their own. The nurses were also taught to auscultate the heart and lungs. Teaching was continued by informal weekly lectures, as well as on the rounds.

At least one physician with special interest in cardiology has constantly been attached to the unit. The day staff consisted of a consultant, a senior and junior registrar.

All patients were clinically examined on admission and thereafter three times daily. Findings including signs of failure and arrhythmias were recorded on occurrence on special time-marked sheets. A bedside chest X-ray was performed on the first morning after admission and repeated when considered necessary. Blood-gas estimations with the patient breathing room air were taken at the same time. Routine ECGs and blood tests including serum enzymes were taken on admission and thereafter each morning.

Treatment

The patients were monitored for at least 48 hours in the 3 bed unit, and, to enable admission of all patients fulfilling the criteria, for at least 4 hours in the bed unit. Also 4 hours were to have passed without sinus bradycardia, AV block II, frequent multifocal, coupled or early ventricular ectopic beats, hypotension and shock. The duration of treatment in the CCU was prolonged by 48 hours following ventricular fibrillation, ventricular tachycardia defined as three successive ventricular beats or more or third degree AV-block.

On admission the patients were given a slow 5.5 per cent glucose drip and humidified oxygen at 4 litres per minute, increased in cases with severe arterial hypoxia. The patients were generally nursed in a propped up position. Diet was light and the patients were encouraged to feed themselves.

Severe pain was treated with analgesic drugs, e.g. oxycodone and pethidine, and more recently pentazocine. Light pain was treated with salicylates. Nitroglycerine was not included in the programme. Anticoagulants (dicoumarol) were given routinely unless considered contraindicated. Heparine was not given.

Treatment of the arrhythmias

The treatment of the supraventricular arrhythmias was primarily guided by the ventricular rates. Atrial fibrillation or flutter with rapid ventricular rates, i.e. over 120 per minute, was treated with digitalis (lanatoside-C 0.4—0.8 mg or ouabain 0.25—0.375 mg intravenously) which if not successful in reducing the ventricular rates, was complemented with DC electroconversion (100 to 400 Joules) under light general anaesthesia. In severe haemodynamic dysfunction electroconversion was immediately performed, occasionally under diazepam sedation. Atrial fibrillation and flutter of long standing were not treated with DC-conversion. Sinus tachycardia with rates over 120 per minute was originally treated with digitalis. During the last year this only led to more frequent pulmonary auscultation and blood pressure controls. Atrial tachycardia was treated with carotid massage and digitalis, and if persisting for over one hour DC conversion. In atrial tachycardia with block digitalis was withdrawn and potassium supplements were given.

Nodal rhythm and AV-dissociation was treated with digitalis withdrawal and atropine sulphate (1.0 mg intravenously) or methyl scopolamine (0.125 to 0.5 mg intravenously). Nodal tachycardia in patients on digitalis was treated with digitalis withdrawl and in patients not on digitalis this was was given when ventricular rates were

over 120 per minute. DC vonversion was per formed if no improvement had been seen after one hour DC-conversion was immediately performed in the presence of cerebral symptoms, hypotension, heart failure or anginal pains

Supraventricular bradycardia with ventricular rates lower than 50 per minute and cases with cerebral symptoms in association with ventricular rates lower than 80 per minute was treated with digitalis withdrawl and atropine sulphate or methylscopolamine. In exceptional cases, resistant to therapy treatment with artifical endocardial pacing was performed with a bipolar electrode introduced via an external jugular or antecubital vein Sinus arrest of more than 3 seconds was managed with digitalis withdrawl and atropine or methyl scopolamine.

Treatment of both first and second degree AV block was managed by the withdrawal of digitalis. This was supplemented with intravenous atropine or scopolamine, and when required n second degree AV-block with isoprenaline infusions. Third degree AV-block was nearly always treated with an on demand endocardial pacemaker system. I cases with ventricular standstill blows on the chest were given and atropine or scopolamine, adrenaline, transthoratic and/or transvenous pacing as well as external cardiac massage, artificial ventilation and bicarbonate infusions. Transvenous on demand pacing was continued in all cases until a satisfactory supraventricular rhythm had been restored for at least 48 hours.

Ventricular ectopic beats at ates of more than 5 per minute, or coupled, or multifocal, or early (R on T phenomenon) and ventricular tachycardia were treated with intravenous lignocaine 50 to 100 mg as a bolus dose followed by infusion of 1 or 2 mg per minute

Persistent ventricular tachycardias, unresponsive to lignocaine therapy were treated with DC-conversion (100 to 400 Joules) Recurrent ventricular arrhythmias led to attempts with other antiarrhythmic drugs including procaine amide, diphenyl hydantoin, quinidine and/or β adrenergic blocking drugs. Patients who during their stay in the CCU had developed entricular tachycardia were nearly always given quinidine for the rest of hospitalization. Ventricular fibrillation was treated with DC conversion (400 Joules) repeated as necessary and supplemented with lignocaine and other antiarrhythmic therapy as required.

Treatment of hypotension and shock

Hypotension defined as a systolic blood pressure below 90 mmHg was managed with atropine or scopolamine unless rapid ventricular rates were present. This was supplemented by rapid intravenous glucose infusions (300 ml) usually under central venous pressure control. When clinical signs of shock including cold skin, deterioration of sensorium, or oliguria in association with a systolic blood pressure below 90 mmHg was present this treatment was supplemented with increased amounts of oxygen, sodium bicarbonate infusions, isoprenaline or noradrenaline infusions.

T eatment of heart failure

Heart failure, as defined by the presence f more than a few scattered basal rales, was primarily treated with intravenous diuretic therapy (frusemide 10 to 40 mg or ethacrynic acid 25 mg) and during the earlier part of 1968 also with digitalis. The head of the bed was raised Treatment was given in relation to clinical findings and discontinued in the absence of signs of heart failure even if the patients had previously been on d gitalis and/or diuretics. Previous digitalis or diuretic therapy was generally reinstituted on discharge from the CCU

Patients with fulminating pulmonary oedema were given digitalis and diuretics, increased amounts of oxygen, treatment being supplemented with oxycodon, theophylline, a sitting position and occasionally venous occlusion of the extremities as well as manually assisted ventilation. Tracheostomy and respirator treatment after transfer to the post operative intensive care unit was resorted to in some cases of intractable pulmonary oedema and severe hypoxia.

After-care

When the smaller unit was in use, after-care was a function of the conventional wards. When the 7 bed unit came into use patients with ventricular

tachycardia and fibrillation, AV-block III or very extensive infarctions were treated in rooms adjacent to the CCU. In uncomplicated cases, patients were mobilized successively with the aid of a physiotherapist towards the end of the first week or beginning of the second, and then encouraged to become increasingly physically active. The patients were discharged towards the end of the third week, after having been accustomed to climbing stairs by themselves.

INVESTIGATIONS

Electrocardiography

Routine 12 lead ECGs including leads, I, II, III, aVR, aVL, aVF, CR_4R, CR_1 $_{4,5}$ and $_7$ were taken an ink-jet recorder (Mingograph, Elema Schönander Stockholm). Supplementary investigation using oesophageal or right atrial electrodes was occasionally performed for further diagnostic evaluation.

Chest X-ray

Bedside anteroposterior chest X-ray films at a tube-film distance of 130 cm, as well as lateral views with a tube-film distance of 150 cm were taken and interpreted by observers unaware of the clinical condition of the patients. This examination was performed by the staff of the Department of Radiology, Serafimerlasarettet.

Blood gas analysis

Arterial blood was used and only values obtained from patients who could be taken off their additional oxygen supply are included. The specimens were analyzed polarographically. PaO_2 was determined with an electrode according to Clark (1956) (Radiometer, Copenhagen). Determinations were performed in the Clinical Physiological Laboratory at Serafimerlasarettet (normal values ≥ 80 mmHg).

Serum enzyme estimations

Blood for enzyme estimation was taken on admission and on following mornings for at least 3 days. The following enzymes were routinely estimated: serum aspartate aminotransferase (GOT), serum alanine aminotransferase (GPT), lactic dehydrogenase (LDH) and its isoenzymes LD_1 and LD_2 as alfa-hydroxybutyrate dehydrogenase (HBD). Reagents were from AB Kabi, Stockholm, and the methods were modified from Wroblewski and LaDue (1955 a) and Wroblewski and LaDue (1955 b). The analyses were performed in the Clinical Chemical Laboratory at Serafimerlasarettet.

When reference is made to maximum GOT values only those obtained 18 hours or later and within 48 hours of onset of symptoms leading to admission are taken into account.

Statistical methods

Conventional methods have been used for the calculation of the arithmetic mean and standard deviation (S.D.). Significance of differences between mean values was tested by Student's t-test. The Chi square test was used for testing the significance of differences of relative numbers. Yates correction was applied when small numbers were employed. Degrees of significance were tested at the 5, 1 and 0.1 per cent level.

Age has been calculated from 10 year class means.

Data registration

The relevant findings for each patient were directly registered into specially constructed registration charts in numerical form (Lundman et al. 1968) and subsequently transferred to punch cards for evaluation by a computer. Every chart was checked against information available following the patients' discharge from the CCU by the physicians attached to the unit. The information in the CCU chart was supplemented after the patients' discharge with information gleaned from the ordinary hospital records. The author has in every instance rechecked all charts against the hospital records, a colleague being present for confirmation.

Autopsy

This was performed in the Pathology Department, Serafimerlasarettet. The examination included an estimation by the pathologist of the extent of the left ventricular myocardium affected

by infarction expressed in per cent. The age of the infarct was also assessed. Mean infarction size was calculated from 10 per cent class means.

Diagnostic criteria

On the basis of daily ECGs and serum enzyme determinations the patients fulfilling any of the admission criteria received either of the following diagnoses acute infarction, suspected infarction or "observation case

The criteria for the diagnosis of acute myocardial infarction in these patients have been the fulfillment of a, b or c.

a) appearance of a pathologic Q-wave, and/or appearance or disappearance of a localized ST elevation followed by a T inversion in two or more of the 12 leads.

b) two GOT values of 40 units or more and with a maximum about 24 hours after onset of symptoms in combination with lower GPT values with a maximum after about 36 hours and/or two HBD-values exceeding 75 per cent of corresponding LDH values higher than 40 units, with a maximum about 60 hours after the onset of symptoms, or a combination of one GOT-GPT value and one HBD-LHD combination, elevated as stated above

c) findings at autopsy of myocardial necrosis of an age corresponding to the onset of symptoms.

Infarction site

The sites of infarction were localized from changes observed in the daily 12-lead ECGs They were coded as being either anterior anterolateral, lateral, posterior, posterolateral, anteroposterior or anteroposterolateral.

On occurrence of the ECG criteria for infarction in two leads or more as explained above in leads CR_{1-5} the site of infarction was designated as being anterior if in leads VL, I and CR_7 it was lateral, if in II, III and aVF it was posterior Combination sites were determined according to the same criteria.

DEFINITIONS

In the following discussion only left heart failure as recorded on admission and during the first 24 hours in the CCU will be considered The following definitions were used

Previous heart failure—A history of digitalis therapy or diuretic therapy not given for hypertension.

Left heart failure—This was diagnosed in patients with one or more of the following findings basal rales, a third heart sound, chest X ray findings of central vascular enlargement, peripheral vascular enlargement and/or confluent areas compatible with pulmonary oedema.

The following grading of the severity of left heart failure has been used

Mild left heart failure—Cases with a few basal rales and/or a third heart sound in association with a normal chest X-ray and no treatment.

Moderate left heart failure—Cases who were treated with diuretics and/or cardiac glycosides in presence of more than a few basal rales but normal chest X-ray findings.

Severe left heart failure—As for moderate left heart failure but with the addition of radiological signs of left heart failure.

Frank pulmonary oedema.—Patients with rales heard all over the chest in association with frothy sputum.

Hypotension and shock per se are not discussed under the heading of left heart failure for the purposes of the present study

Survival

Patients are considered to have survived their myocardial infarction if they were

a) discharged alive from hospital

b) alive in hospital 8 weeks after date of admission

c) readmitted to the CCU for a subsequently verified reinfarction.

RESULTS

General findings

During the period studied there were 888 admissions to the CCU 363 of these (41 per cent) fulfilled the criteria for a diagnosis of acute myocardial infarction. In the following each of these admissions will be referred to as different patients The number of different individuals with confirmed infarcts was 326

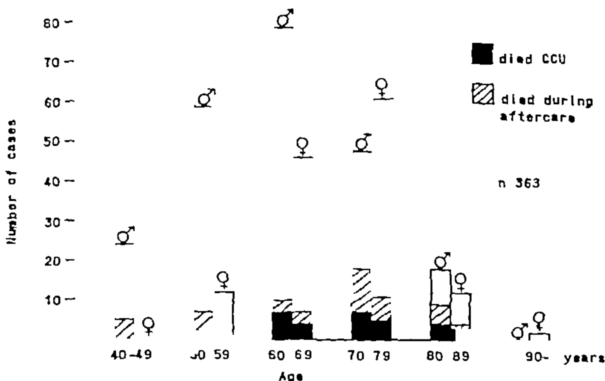


Fig. 1 Relationship between mortality and age in 363 patients with acute myocardial infarction treated in CCU and subsequently in general hospital wards

There were 228 (63 per cent) men with a mean age of 63.5 years S.D = ±16.6, and 135 women (37 per cent) with a mean age of 69.7 S.D = ±9.9 giving a male female ratio of 1.7 and a total mean age of 66.2 years, S.D = ±11.1 The age distribution is presented in Fig. 1 which also includes the CCU and total hospital mortality Of the 363 patients 33 (9 per cent) died during the CCU stay and a further 39 patients (11 per cent) died during their aftercare in the wards giving a hospital mortality of 72 (20 per cent) The mean lenght of CCU care was 50 hours, S.D = ±16.2 and that of total hospital care 23 days.

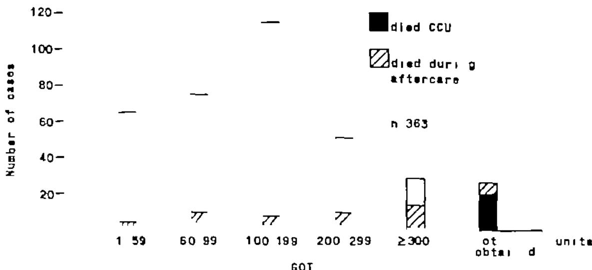
The male CCU death rate was 9 per cent and the total hospital mortality was 22 per cent. These mortality rates do not differ significantly from those of the women, of whom 10 per cent died in the CCU and total hospital mortality was 17 per cent ($P > 0.05$)

The mortality in the 143 patients aged ≥70 years was 29 per cent and was significantly higher than that of the 220 patients aged <70 years which was 14 per cent ($P < 0.001$)

The time between onset of symptoms and admission to the CCU was not to exceed 48 hours The mean delay period was 11 hours. 40 per cent had arrived to the CCU within 3 hours, and 85 per cent had arrived within 24 hours. The remainder arrived during the second day of their illness, no exact information being given by 13 patients.

Enzymes

Only GOT maximum levels will be considered. Fig. 2 shows the distribution of the GOT levels and concomitant mortality No GOT levels were obtained in 26 subjects as these died before the maximum value had been reached The fact that 6 of these survived their CCU stay is explained by their transfer to the postoperative intensive care unit for respirator care where they subsequently died before maximum GOT levels could be obtained



F g 2 Relationship between mortality and GOT maximum level in 363 patients with acute myocardial infarction treated in CCU and subsequently in general hospital wards

A significantly higher mortality was found in the 80 patients with GOT ≥200 (30 per cent) as compared to that of the 257 patients w th GOT <200 units (9 per cent) ($P<0\ 001$)

Infarction site

The findings are given in Table 1 There was no association between infarction site and mor tality ($P>0\ 05$) The diagnosis of an infarction extending over the anterior, lateral as well as posterior walls of the left ventricle, referred to as combined in the table, is open to criticism and part of the ECG changes although fulfilling the criteria previously given may be due to secondary pericarditis.

Mode of death

Of the 72 patients who died, the deaths of 17 were unattended or information was inadequate. I 15 patients (27 per cent) the most prominent symptoms and signs starting the terminal stages were those of frank pulmonary oedema, and in 20 patients (36 per cent) shock. Abrupt cessation of the circulation not associated with shock or pul monary oedema accounted for the deaths of 20 patients, 8 with asystole and 8 with ventricular fibril lation. Left ventricular rupture and cardiac tamponad occurred in 4 patients.

Size of nfarct n at autopsy as compared to mode of death

I 62 of the 72 deaths the pathologist was abl to giv an estimate of the total size of infarction ld as well as recent, in per cent of the left ventri cular myocardium. The mean infarction size of those 12 who died in pulmonary oedema (73 per cent, S D $=\pm 24$) did not differ significantly from the infarction size for the subjects who died in shock (64 per cent, S.D $=\pm 17$) ($P>0.05$)

TABLE 1 Infarction site according to ECG with mortality

Location	No of patients	Per cent	Mortality per cent
Uncertain*	148	41	20
Anterior	85	23	20
Anterolateral	26	7	23
Posterior	53	15	23
Posterolateral	29	8	17
Anteroposterior	6	2	33
Lateral	12	3	0
Combined*	4	1	0
Total	363	100	20

Includes bundle branch block nd subendocardial infarction

Indicates ECG changes over anterior posterio and lat eral all

TABLE 2 Left heart failure on admission in relation to CCU, after-care and total hospital mortality

	No failure		Failure		
	Survived	Died	Survived	Died	P
CCU-care	199	9	131	24	<0 001
After-care	183	16	108	3	<0 01
Total hospital care	183	25	108	47	<0 001

On the other hand the mean size of infarction for those dying in shock and pulmonary oedema (67 per cent, S D $= \pm 20$) was significantly larger than the infarctions of those dying in asystole, ventricular fibrillation and ventricular rupture (54 per cent, S.D $= \pm 18$) ($P < 0\ 05$)

Findings related to left heart failure on admission

Past history in relation to signs of left heart failure on admission There was a significant association ($P < 0.05$) between the incidence of left heart failure on admission and a history of failure (56 per cent against 33 per cent) but not as regards previous myocardial infarction, angina pectoris or treated hypertension

Left heart failure on admission to the CCU

Left heart failure on admission was found in 155 (43 per cent) out of the 363 patients. In 30 of the 155 cases frank pulmonary oedema was diagnosed. The associated CCU mortality was 15 per cent (24/155) This is significantly higher than the 4per cent of those without failure as illustrated in Table 2 ($P < 0.001$) Correspondingly there was a significant increase in after-care mortality 18 against 8 per cent ($P < 0\ 01$)

Consequently the total hospital mortality also differs significantly (30 per cent against 12 per cent) ($P < 0\ 001$)

Table 3 shows the corresponding figures with the patients grouped according to a negative or positive history of previous heart failure. Previously compensated patients do not differ in total hospital mortality (18 per cent) from those with a history of heart failure (22 per cent) ($P > 0\ 05$)

In the previously compensated group a significant association between findings of heart failure on admission was found with CCU mortality ($P < 0\ 001$) but not as regards after-care mortality ($P > 0\ 05$) When considering the patients with previous heart failure, no significant relationship between admission findings of left heart failure and CCU mortality was seen ($P > 0.05$)

Of the 30 patients with frank pulmonary oedema on admission one had associated hypotension and 3 were in shock. Of those other 125 patients with signs of failure two had associated hypotension and 11 were in shock.

TABLE 3 Left heart failure on admission in relation to CCU, after-care and total hospital mortality for previously compensated patients and those with history of heart failure. Figures in brackets denote patients with frank pulmonary oedema

		No previous heart failure		Previous heart failure	
		No failure	Failure	No failure	Failure
CCU-care	Survived	137	55 (8)	62	76 (19)
	Died	4	14 (2)	5	10 (1)
	P	<0 001		>0 05	
After-care	Survived	125	47 (6)	58	61 (15)
	Died	12	8 (2)	4	15 (4)
	P	>0 05		<0 05	
Total hospital care	Survived	125	47 (6)	58	61 (15)
	Died	16	2 (4)	9	25 (5)
	P	<0 001		<0 05	

TABLE 4 Left heart failure during first 24 hours in CCU in relation to total hospital mortality

Degree of failure	No of patients	Died	Per cent
None	122	10	*8*
Mild	55	10	*18*
Moderate	73	14	*19*
Severe	73	23	*32*
Frank pulmonary oedema	40	15	*38*
Total	363	72	*20*

Left heart failure during first 24 hours in the CCU

Signs of left heart failure during the first 24 hours in the CCU were found in 241 of the 363 patients (66 per cent) Of these 241 patients 26 per cent died, which is significantly higher than 8 per cent of those without signs of left heart failure ($P<0.001$) Table 4 shows the mortality for the whole patient group in relation to the degree of left heart failure.

The 153 patients with previous heart failure showed a significantly greater tendency to be in left heart failure (79 per cent against 57 per cent) ($P<0.001$) This was not due to a higher prevalence of larger infarcts in those with previous heart failure, the opposite being the case (see page 19) The prevalence of left heart failure increased from 43 per cent on admission to 66 per cent during the first day in hospital. The total hospital mortality was significantly higher for those with signs of left heart failure on admission (30 per cent) than for those developing these during the first 24 hours (17 per cent) ($P<0.05$)

The prevalence of left heart failure during the first 24 hours in the patients with and without previous heart failure is shown in Table 5 which also gives the CCU after-care and total hospital mortality

A similar pattern to that obtained in analyzing admission findings of left heart failure as regards CCU after-care and total hospital mortality in relation to the past history was found.

Severe heart failure and frank pulmonary oedema in previously compensated subjects carried a mortality of 38 per cent as compared to 15 per cent of those with mild and moderate left heart failure ($P<0.01$) When considering those with a history of heart failure no such difference emerged, as 30 per cent of those with severe failure and frank pulmonory oedema died compared to 24 per cent of those with mild or moderate left heart failure ($P>0.05$)

Of the 241 patients with failure 23 (10 per cent) also showed signs of shock. This includes 6 who had frank pulmonary oedema.

Left heart failure in relation to age and sex

The mean age for the 363 patients was 66.2 years, S.D $=\pm11.1$ The mean age of those with previous heart failure was 70.3 years, S.D $=\pm9.7$ which differs significantly from 63.2 years, S.D $=\pm10.3$ for those previously compensated ($P<0.001$)

Table 6 shows the tendency of left heart failure to increase with increasing age. The male/female ratios are also included in Table 6. It is seen that the patients with a history of heart failure as well as being older include significantly more women (50 per cent) as compared to those previously compensated (28 per cent) ($P<0.001$)

Left heart failure in relation to mode of death

Of the 40 patients with frank pulmonary oedema during the first 24 hours 15 (38 per cent) died Eleven of these 15 died in pulmonary oedema and 3 with shock. No other relationship between findings of heart failure and mode of death was found.

Left heart failure in relation to infarct size at autopsy

In 62 of the 72 patients who died an autopsy was performed and an estimate made of the size of the recent infarct. The mean infarct size in this group was 47 per cent of the left ventricular myocardium. Of 45 patients in whom less than 50 per cent of the left ventricle was infarcted, 84 per cent had clinical left heart failure during the first 24 hours in the CCU and this incidence did not differ from that of 88 per cent in the 17 patients with larger infarcts.

TABLE 5 Lef heart failure dur g the first 24 hours the CCU relation t CCU fter-care and total ho pital mortality in pr io sly compensated patients and in tho th history of heart failure

		No previous heart failure						Previous heart f il re					
			F lure						F ilure				
		No failure	All	Mild	Moderate	Severe	Pulmonary oedema	No failure	All	Mild	Moderate	Severe	Pulmonary oedema
CCU-care	Alh	87	105	35	32	27	11	31	107	13	33	58	23
	Dead	3	15	4	2	6	3	1	14	3	6	2	3
	Mortality per cent	*3*	*13*	*10*	*6*	*18*	*1*	*3*	*12*	*19*	*15*	*5*	*12*
	P	<0 05						>0 05					
After-care	Alh	81	91	32	30	22	7	31	88	13	29	8	18
	Dead	6	14	5	2	5	4	0	19	0	4	10	5
	Mortality per cent	*7*	*13*	*9*	*6*	*19*	*36*	*0*	*18*	*0*	*12*	*76*	*22*
	P	>0 05						<0 05					
Total hospital care	Alh	81	91	32	30	22	7	31	88	15	29	28	18
	Dead	9	29	7	4	11	7	1	33	3	10	12	8
	Mortality per cent	*10*	*24*	*18*	*1*	*35*	*30*	*3*	*27*	*19*	*76*	*30*	*31*
	P	<0 01						<0 01					
	Total	90	120	39	34	55	14	32	121	16	39	40	26

TABLE 6 Left heart failure during first 24 hours in CCU in relation to age and sex

		Total	No failure	Failure			
				Mild	Moderate	Severe	Pulmonary oedema
All patients	Number	363	122	55	73	73	40
	Mean age, yrs.	66 2	62.0	62.9	67 8	69.5	72.5
	SD	10 7	9.2	11.0	9 7	10 6	9.6
	Male/female ratio	1 7	2.5	1.8	1 8	0 9	1 5
No previous failure	Number	210	90	39	34	33	14
	Mean age, yrs.	63 2	61.2	60 1	65 7	66 6	70.2
	SD	10 3	9.2	10 4	9.8	10 5	11.8
	Male/female ratio	2.6	3 1	2.9	3 3	1.2	3 7
Previous failure	Number	153	32	16	39	40	26
	Mean age, yrs	70.3	64 2	69 5	69 6	73.8	73 7
	SD	9 7	8 5	9 7	9 4	9.6	7 9
	Mal /female ratio	1.0	1 5	0 6	1 2	0.7	1.0

If those 35 patients with o previous history of cardiac decompensation are considered separately 72 per cent of those with less than 50 per cent of the left ventricle involved (25 patients) developed heart failure as compared with 90 per cent of those with more than 50 per cent involvement (10 patients) This difference was significant ($P<0.05$) There were no differences in the group of 27 patients with a previous history of decompensation.

When both old and recent infarcts are considered in the 62 patients, the mean area of the left ventricle involved was 62 per cent. The incidence of heart failure did not differ when they were separated into those with more or less of the left ventricle involved.

Left heart failure in relation to GOT maximum

Infarction size has been found to be related to enzyme levels (Kibe & Nilsson 1967) Some confirmation is obtained in the present material from those instances where maximum GOT values as well as an estimate by the pathologist as regards the size of recent infarction was available (=0 37 $P<0.05$) The incidence of heart failure in patients with a GOT maximum <100 units (56 per cent) was significantly lower than that found in those with higher GOT maximum (70 per cent) ($P<0.01$) The infarction size as a determinant factor in left heart failure was investigated by comparing the incidence of heart failure in relation to GOT maximum, as shown in Table 7

No relation between severity of heart failure and enzyme levels was found. Although signs of failure were significantly more common in the patients with history of heart failure, they had a significantly higher incidence f smaller infarcts, i.e. GOT <100 units, of 53 per cent as compared to 34 per cent in those previously compensated ($P<0.001$)

Left heart failure in relation to infarction site

In 215 patients the ECG findings allowed for localization of the infarct, and the findings are presented in Table 8.

There was a higher rate of left heart failure (71 per cent) in patients with predominantly anterior infarctions as compared to in those with predominantly posterior infarcts (51 per cent ($P<0.01$) This difference remained in the previously compensated patients separately ($P<0.05$) but not in those previously in failure.

The reason for this difference between anterior and posterior infarctions is not due to a higher incidence of larger infarctions (GOT ≥100) n

TABLE 7 Left heart failure [illegible] first 24 hours in CCU [illegible] relation to GOT maximum for patients with and without previous heart failure

GOT (units)	No previous failure					Previous heart failure				
			Failure					Failure		
	No of patients	No failure	All	Mild and moderate	Severe and pulmonary oedema	No. of patients	No failure	All	Mild and moderate	Severe and pulmonary oedema
1— 59	31	18	13	8	5	34	11	23	9	14
60— 99	35	23	12	10	2	4	10	32	19	13
100—199	73	32	41	26	15	42	6	36	17	19
200—299	35	12	23	16	7	16	4	12	5	7
≥300	20	4	16	5	11	9	0	9	2	7
Not available	16	1	15	8	7	10	1	9	3	6
Total	210	90	120	73	47	153	32	121	55	66

) GOT values not accepted as patients died before maximum values were available.

those predominantly anterior (70 per cent) as compared to those with posterior infarctions (73 per cent) ($P>0.05$)

Left heart failure in relation to arterial hypoxia

PaO_2 in patients taken while breathing room air could be determined in 297 (82 per cent) of the patients.

The results appear in Table 9 which shows that the incidence of $PaO_2 \leq 60$ mmHg in patients with failure (36 per cent) is significantly higher than that among the patients without failure (15 per cent) ($P<0.001$) Again when splitting up the group this difference remains significant for those previously compensated but not for those with a history of heart failure.

Additional findings with bearing on left heart failure

A murmur compatible with a diagnosis of mitral incompetence was heard in 28 (8 per cent) of the 363 patients. Of these 28 patients, 7 belonged to those previously compensated, whereas 21 had a history of previous heart failure ($P<0.001$) In 3 instances the murmur was not present on admission but appeared during the first 24 hours. In two other patients mitral incompetence was associated with frank pulmonary oedema.

Atrial fibrillation or flutter either transient or constant during the first day in the CCU was observed in 19 per cent of the patients. In 11 instances it was seen among the 122 patients without left heart failure, and in 58 instances among the 241 with signs of failure ($P<0.001$) The incidence of these arrhythmias in the previously compensated group was 13 per cent and differed significantly from 28 per cent of those 153 patients with a history of heart failure ($P<0.001$)

DISCUSSION

At the Edinburgh symposium on acute myocardial infarction Meltzer said (1967) that the similarity in mortality figures reported from several CCUs merely reflected a uniform ability to prevent arrhythmic deaths and a uniform inability to combat death from power failure

TABLE 8. Left heart failure during first 24 hours in CCU in relation to ECG site of infarction

		Site of infarction					
	Clinical findings	Anterior + Anterolateral	Posterior + Posterolateral	Lateral	Antero-Posterior	Combined	Uncertain
All (n=363)	No failure	32	40	3	2	2	43
	Failure	79	42	9	4	2	105
No previous failure (n=210)	No failure	30	35	3	1	2	19
	Failure	56	27	6	4		25
Previous failure (n=153)	No failure	2	5	0	1	0	4
	Failure	23	15	3	0	0	80

TABLE 9 Incidence of hypoxia in relation to findings of left heart failure during the first 24 hours in the CCU

PaO_2 (mmHg)	All patients		No previous heart failure		Previous heart failure	
	No failure	Failure	No failure	Failure	No failure	Failure
≤60	15	71	9	32	6	39
>60	86	125	68	71	18	54
P	<0 001		<0 01		>0 05	

Further improvement in the care of patients with acute myocardial infarction will therefore in part have to be achieved in the group with heart failure.

Incidence of left heart failure

The mortality in the present CCU series was of the same order as reported from similar units abroad (Killip & Kimball 1967 Lawrie et al. 1967 Lown et al. 1967 MacMillan et al. 1967 Restieaux et al. 1967 Meltzer 1968 Sloman et al. 1968 and Thomas et al. 1968)

Left heart failure on admission was found in 43 per cent of the patients and the incidence rose to 66 per cent during the course of the first 24 hours in the CCU

Haemodynamic changes have been registered to occur within minutes of experimental infarction in animals (Hood et al. 1969) and if the same is the case in man it would suggest the presence of a time-lag between haemodynamic alterations and the development of clinical findings of left heart failure

The incidence of left heart failure of 66 per cent is in accordance with several recent reports from CCUs, which on the other hand refer to total CCU stay The range of incidence according to previous publications lies between 47 to 67 per cent (Julian et al. 1964, Lown et al. 1967 Restieaux et al. 1967 Bergqvist et al. 1968 Meltzer 1968 and Thomas et al. 1968)

The incidence of 11 per cent of frank pulmonary oedema during the first 24 hours is also in accordance with the figures given i the literature of 5 to 16 per cent (Wallace et al. 1967 Lown et al. 1967 and Bergqvist et al. 1968)

Left heart failure in relation to mortality

Left heart failure on admission or during the first 24 hours in the CCU was associated with an increased mortality

A striking finding on mortality was that left heart failure on admission and during the first 24 hours was associated with a poor CCU prognosis but not as regards after-care in those previously compensated Those with a history of heart failure on the other hand had a significantly higher death rate in the after-care period, the total hospital mortality not differing between these groups. No distinct relationship between a finding of heart failure and mode of death was found in this study which is in agreement with Norris et al. (1968)

Relationship between infarction size to left heart failure

An increasing incidence of left heart failure with increasing infarction size was found for the whole group as judged by GOT maximum values as well as estimated at autopsy for those previously compensated. This relationship between the incidence of left heart failure and GOT maximum values was valid only for those previously compensated. No reports for comparison were found in the literature.

The finding is parallel to that described in Part II where a significant correlation between GOT levels and pulmonary artery diastolic pressures is described

Left heart failure and arterial hypoxia

A higher incidence of more severe degrees of arterial hypoxaemia was found in the present study in patients with signs of left heart failure when compared with those without. This finding was also primarily based on the results obtained in the patients without a history of previous heart failure On the other hand as blood gas estimations had been performed significantly more often on those patients who previously had been compensated a comparison with the findings in those with a history of failure becomes less suitable More severe degrees of arterial hypoxia associated with findings of failure in acute myocardial infarction have previously been reported (Valentine et al 1966 Buschman et al 1967 Shapiro et al. 1968 and Storstein & Rasmussen 1968)

General findings

The relationship found between increasing age and increasing severity of left heart failure is in accordance with Master et al (1937) Furthermore the patients with a history of heart failure differed from those previously compensated in being significantly older and including significantly more women

SUMMARY

Left heart failure in patients with acute myocardial infarction treated in a CCU has been studied in 363 consecutive patients The study was limited to an evaluation of heart failure during the first 24 hours in hospital. 43 per cent of the patients were in failure on admission and this figure rose to 66 per cent during the first 24 hours in hospital. The presence of heart failure was associated with an increase in mortality although the rise in incidence of failure observed during the first day did not carry a proportional increase in mortality

A differential analysis of findings depending on whether the patients were compensated prior to admission has been employed An important finding which may effect the routine management of these patients is that heart failure in previously compensated patients carries a high CCU mortality whereas failure in patients with a past history of decompensation is associated with an increased after-care mortality The total hospital mortality did not differ between these two groups.

Furthermore, it was found that the significant higher incidence of larger infarcts, arterial hypoxia and anterior infarcts as opposed to posterior infarcts in patients with failure reflected findings which were significant in only the group which previously had been compensated.

PART II

STUDY OF THE CENTRAL HAEMODYNAMICS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH SPECIAL REFERENCE TO THE PULMONARY ARTERY DIASTOLIC PRESSURE

The aim of this part of the present study was to measure pulmonary artery pressures, with special reference to the diastolic pressure, in subjects with acute myocardial infarction, and to relate these pressures to different clinical and laboratory parameters.

A high incidence of pulmonary hypertension in acute myocardial infarction has previously been reported by Fluck and co-workers (1967). On the other hand no detailed study has been presented to date relating the pulmonary artery diastolic pressures (PAdp) which probably best reflect left heart filling pressures (see below) to the clinical and laboratory parameters which characterize an acute infarction. Furthermore, with the increased mortality associated with left heart failure in this condition, improved knowledge of the different aspects of this complication is needed.

MATERIAL AND METHODS

The patients included in this part of the present investigation were admitted to the coronary care unit (CCU) from March 1968 to November 1969. The general methods used in this unit, including criteria for admission, diagnosis and routine investigations have been presented previously (page 9 to page 13).

Patient selection

Patients included in this study had ECG evidence suggesting acute myocardial infarction and were to be in sinus rhythm. They were excluded if they had history suggestive of previous heart failure, i.e. dyspnoea on walking on the flat, or dependant oedema. N patient was studied who had received digitalis previously nor those who had received diuretics unless a clear history was obtained that they had been used in the treatment of moderate hypertension. Similarly patients with increased heart size on previous chest X rays were excluded. None of the patients had sustained a previous myocardial infarction within a period of 3 weeks before the present episode. Patients with cardiac murmurs, pericarditis or a history of chronic bronchitis or pulmonary emphysema were excluded as were those who had persistent systolic hypotension (<90 mmHg).

All patients fulfilling the above criteria were studied providing they were admitted to the unit and the author was available. If more than one patient became available simultaneously the one with the lowest room number in the unit was studied. The allocation of patients to rooms was outside the author's influence.

Patients

Pulmonary artery catheterization was attempted 71 instances of suspected acute myocardial farction.

Failure to reach the pulmonary artery with the float catheter was encountered in 6 instances and 4 patients refused catheterization.

In 11 cases the suspicion of an acute myocardial infarction could not subsequently be verified when serial ECGs and serum enzymes were available. The results in 50 episodes of myocardial infarction 49 patients will be presented. One patient was vestigated twice for successive infarctions. For convenience they are referred to as 50 different patients in the text. A brief summary of the salient features in these cases is presented in Table 10. There were 35 men with an average age of 58 years, 40 to 78 years, and 15 women with an average age of 66 years, range 55 to 76 years. In these

TABLE 10. Salient features of the 50 cases of acute myocardial infarction investigated with pulmonary artery catheterization

	Mean	Range	S D	Number
Age	60	40—78		
Delay* (hours)	20	4—56	10	
GOT max. (units)	180	37—550	102	
PaO_2 (mmHg)	71	41—104	13	
Predominant site of infarction				
Anterior				27
Posterior				19
Lateral				3
Combined				1

) Time interval between onset of symptoms and catheterization

) Value obtained immediately prior to catheterization

50 patients typical enzyme patterns consistent with acute myocardial infarction were seen in all who survived long enough for this to be possible except one (No. 13) Characteristic ECG changes consistent with recent myocardial infarction according to the criteria given in Part I, page 13 were seen in all with the exception of patient No. 30 who had a marked ST T depression in the anterior chest leads suggesting a subendocardial infarct. Of these infarcts 27 were predominantly anterior 19 posterior 3 lateral and in one instance combined antero-postero-lateral, although part of the ECG changes in this patient may alternatively be explained by secondary pericarditis.

Eight patients died during the hospital stay which averaged 20 days (range 1 to 35 days) giving a mortality of 16 per cent. Five patients (10 per cent) died in the CCU In the 8 cases who died autopsy confirmed the diagnosis of an infarction consistent in its appearance with the date of onset of symptoms as judged by an experienced pathologist. Three patients died of left ventricular rupture and cardiac tamponade. One died in shock after developing severe mitral insufficiency due to rupture of a papillary muscle. One patient died in frank pulmonary oedema and asystole Two died in progressive heart failure associated with arterial hypoxia and one subject died from ventricular fibrillation due to reinfarction.

The interval between onset of symptoms which had led to hospital admission and the time for pulmonary artery catheterization averaged 20 hours, range 4 to 56 hours. Eleven patients were investigated within 12 hours of the onset of symptoms, 28 between 12 and 24 hours, 8 between 25 and 36 hours and two between 37 and 48 hours and one 56 hours after onset.

Of the 50 patients 5 had a history of one previous myocardial infarction treated in hospital, 15 had a history of angina pectoris on effort for more than one month before the admission, 11 had received previous treatment for moderate hypertension and 3 gave a history of diabetes mellitus.

HAEMODYNAMICS

Pulmonary artery and aortic pressures were measured when at least 30 minutes had passed after the insertion of the catheters. Pain requiring the administration of analgesics was to have subsided. At least 4 hours were to have passed following the last administration of oxycodone, pethidine and pentazocine At least 12 hours were to have passed since the last administration of procainamide and at least 24 hours after the last administration of diphenylhydantoin. If patients were on lignocaine administration this was stopped 30 min. prior to measurements. The catheters were flushed intermittently with heparinized normal saline.

Haemodynamic measurements were carried out with the patient receiving additional humidified oxygen at a rate of 4 to 6 liters per min. administered either through a face mask or a naso-pharyngeal catheter The patients were studied in their beds in the CCU propped up to 30° Pressures are given with reference point 5 cm below the level of insertion of the 4th rib into the sternum. In addition the antero-posterior diameter of the chest was measured in each instance. (For conversion to midchest measurements 4.5 mmHg are to be added which corresponds to the mean value of the 50 patients investigated)

Before catheterization the procedure was always explained to the patient as well as the purpose of the study Permission to proceed was then asked

for Catheterization was performed after the routine chest X ray examination on the first morning following admission.

PULMONARY ARTERY CATHETERIZATION

This was performed with a 125 cm long, soft flow guided polyethylene catheter PE 60 (Clay Adams, N Y) via an antecubital vein by the Seldinger technique (1953) A local anaesthetic was only occasionally required. After introducing the catheter into the vein it was carefully advanced under ECG and intermittent pressure control. A few ventricular extra systoles, or a short ventricular tachycardia commonly indicated that the right ventricle had been reached The catheter was then advanced 10 cm and the pressures were checked Usually right ventricular or pulmonary artery pressures had been obtained. If the pulmonary artery had not been reached the catheter was retracted for some 20 cm, and new attempts were made.

The end of the float catheter was put onto a needle hilt which was attached to a multiple section tap (Ole Dich, Hvidovre, Denmark) which in turn was connected to a pressure transducer (EMT 34, Elema-Schönander Stockholm) The recordings were obtained by an ink jet recorder Mingograf 81 (Elema Schönander, Stockholm) The whole system, e. catheter needlehilt, tap and transducer was tested and found to have flat response up to a frequency of 10 cycles per sec.

A hydrostatic standard corresponding to a pressure of 20 mmHg above the zero line was used as reference. Mean pressures were obtained by electrical integration. Values from at least 2 respiratory cycles and at least 10 heart beats were measured to obtain pulmonary artery pressures. No measurements were performed during or immediately after micturition, vomiting, coughing or moving. The catheters were left in place for at least one hour in all patients.

COMMENTS

The technique of flow guided catheters was developed by Dotter & Straube (1962) and has since then also been described by Bradley (1964) Fife & Lee (1965) Vogel et al. (1965) and Beregård et al. 1966) It is a technique which is suitable for catheterizing severely ill patients at the bedside with minimal disturbance to the patient. Another advantage is that no radiographic control is required to introduce these catheters

The usefulness has been confirmed by several workers who have employed this method in patients with acute myocardial infarction (Valentine et al. 1966, Flock et al. 1967 Pain et al. 1967 Balcon et al 1968 and Stannard et al 1968) No instance of fatal arrhythmia has been reported by these authors although ventricular ectopic beats and tachycardias may be provoked, as is the case when stiff catheters are used.

In studying left ventricular failure a left heart catheterization would be preferable Although this has been performed in acute myocardial infarction (Kirby et al 1968 Nixon et al. 1968 Nixon 1968, Begg et al. 1969 Hodges et al. 1969 Loeb et al. 1969 and Russell et al 1969) without any harm to the patients these procedures may still be associated with a greater risk and inconvenience. Right sided heart catheterization and pulmonary wedge pressures measurements on the other hand may provide as good information in the absence of increase in pulmonary vascular resistance and can be obtained more easily To obtain a wedge pressure usually requires a stiff catheter and fluoroscopy facilities, and would for the purposes of the present study which in some cases involved measurements over several hours possibly be associated with increased risks to the patient

In contrast the PAdp is easily obtained, and good agreement has been reported between t and left atrial mean pressure as well as left ventricular end diastolic pressure. Kaltman et al. (1966) in a series of 70 subjects found good greement between pulmonary artery diastolic pressures and left atrial mean as well as left ventricular end-diastolic pressures (S.D = 1 6 mmHg) except in 14 subjects whom these authors assumed to have pulmonary vascular disease. Recently Jonsson & Sanai (1970) confirmed this by an investigation of 64 patients with valvular disease n the left heart without pulmonary disease. They found that below 30 mmHg the relationship between PAdp and left atrial mean pressure is good (S.D = 2.74) but

not in patients with severe pulmonary disease. In this study as will be seen, no PAdp above 30 mmHg was encountered

For comparisons between PAdp and left heart measurements it is probably the left atrial mean pressure rather than the left ventricular end diastolic pressure that provides the most suitable parameter for comparison. This may explain the findings of Bouchard et al. (1969) who found that the left ventricular end-diastolic pressures commonly exceeded the PAdp in subjects with impaired left ventricular function.

Extensive studies on the relationship between the PAdp and left heart filling pressures in subjects with acute myocardial infarction have not been performed. In one case included in the investigation of Kirby et al. (1968) the PAdp and left ventricular end-diastolic pressures were identical (23 mmHg) Recently Hodges et al (1969) found satisfactory agreement between raised PAdp and pulmonary wedge pressures in 3 patients with acute myocardial infarction and left ventricular end diastolic pressures in a further two patients.

Normal left atrial pressures in association with pulmonary oedema in a subject with acute myocardial infarction has been described by Nixon (1968) This opinion is based on left heart measurements made in one patient several hours after commencing treatment for acute pulmonary oedema which included positive pressure artificial ventilation and 80 mg frusemide. Since both these interventions may affect left sided pressures this view should be accepted with reservation. Similarly the persistence of radiological pulmonary oedema in this patient may have been due to a time lag between the reduction in left heart pressures and the disappearance of the X ray signs. Little is known about the temporal pattern of X-ray changes in relation to left heart pressure changes.

Normal pulmonary artery pressures according to Jonsson (1967) in healthy elderly subjects with the reference point of 5 cm behind the point of insertion of the fourth rib are as follows

Mean	20 mmHg.	S D = ± 3 0
Systolic	11 mmHg.	S D = ± 2 5
Diastolic	6 mmHg.	S.D = ± 5

The upper limits of normal pulmonary artery pressures obtained by adding two S.D to the mean values are therefore

Systolic	26 mmHg
Mean	16 mmHg
Diastolic	11 mmHg

These pressures have been accepted as the upper normal value in this investigation.

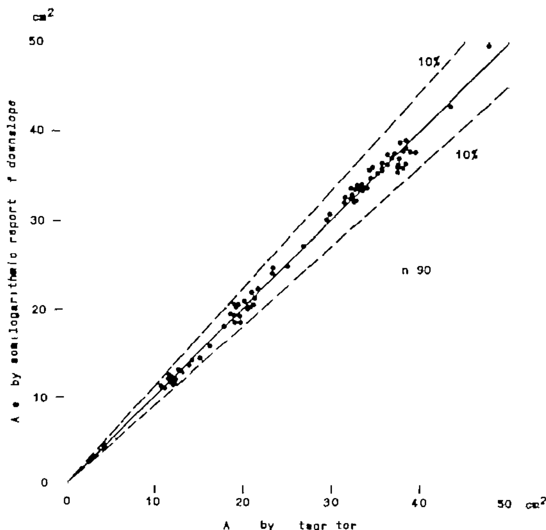
AORTIC CATHETERIZATION

The aortic pressures were obtained through a 75 cm long teflon catheter internal diameter 0 75 mm, (Stille Werner Stockholm) introduced by the percutaneous Seldinger technique (1953) through either the brachial or femoral arteries after infiltration with a local anaesthetic (lignocaine) The catheter inserted into the brachial artery was advanced to the central aorta. In the femoral artery it was advanced for 30 cm.

The arterial catheter together with its attachment system to a multiple section tap (Ole Dich, Hvidovre, Denmark) and pressure transducer (EM 34, Elema Schönander Stockholm) had a flat response to a frequency of 17 5 cycles per sec. A hydrostatic standard corresponding to 100 mmHg above zero line was used as standard reference. Mean pressures were obtained by electrical integration.

CARDIAC OUTPUT

The cardiac output was estimated with the dye dilution method developed by Hamilton and his associates (Hamilton et al. 1928 a, Hamilton et al. 1928 b, Moore et al. 1929 Kinsman et al. 1929 Hamilton et al. 1931) Indocyanine green (Cardiogreen, Hynson, Westcott and Dunning) 5 or 10 mg was injected through the float catheter into the pulmonary artery as rapidly as possible with a tuberculin syringe modified according to Sparling (1961) and Grimby and Nilsson (1963) The forward part of this syringe is extended into a trunk. After all but 1 ml of the syringe has been filled with saline (controlled by a mechanical lock device) dye (5 or 10 mg in 1 0 ml) was drawn to the anterior part of the trunk which is then connected to the float catheter and injected as



F g 3 Plot of the area under 90 dye dilution curves estimated by semilogarithmic replot of downslope and that estimated by the Beckman integrator utilizing the method of Hepner et al. (1964) Lines indicate identity ±10 per cent.

rapidly as possible. On injection the dye is flushed *into the pulmonary artery by the saline following* behind. With the syringe used in this experiment the quantity of dye injected was 0 98 ml (mean of 10 weighings) All calculations have therefore been accordingly corrected

The dye dilution curve was obtained by withdrawing arterial blood through cuvette densitometer by specially constructed pump withdrawing blood at a constant rate of 20.0 ml per min., S.D = ±0 71 (mean of 10 measurements) Calibration was performed for each subject using at least four d fferent dye concentrations.

The dye-curves were estimated with a Beckman Cardiodensitometer (Spenco Division of Beckman Instruments, Inc., Palo Alto California) which involves counting of the curve according to Hepner et al. (1964)

This method of calculating the area under the curve was tested on 90 curves of varying size and the results were compared with those obtained by the conventional method of summing the area under the ascending limb and the semilog replot of the descending limb (Kinsman et al. 1929) The result appears in F'g 3 and shows excellent agreement (r=0 99) The mean curve area as obtained

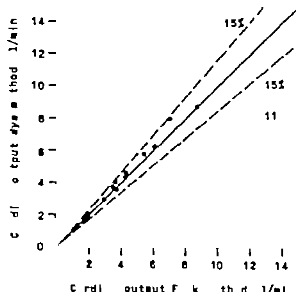


Fig. 4 Plot of cardiac outputs measured by the dye dilution technique and the Fick method in 10 patients (11 estimations). Lines indicate identity ±15 per cent.

by the Integrator for the 90 curves was 28.2 cm², S.D = ±10.0 as compared with 28.3 cm² S.D = ±10.1 with the conventional method.

This method for obtaining the cardiac output with the dye technique was also compared with the cardiac output by the direct Fick method in 11 instances. For this purpose 10 subjects undergoing right heart catheterization at the Clinical Physiological Laboratory at Serafimerlasarettet had their cardiac output determined by both methods. In one case the determination was done both at rest and during exercise and both values have been included to provide one high output value. The first dye curve obtained immediately after the Fick estimation was used for comparison if several curves had been obtained. The results are presented in Fig. 4 showing that in no comparison did the difference fall outside the 15 per cent line ($r=0.99$ $P<0.001$). The mean cardiac output value as obtained by Fick's method was 5.71 liters per min., S.D = ±3.1 as compared to 5.85 liters per min., = ±S.D.2.8 for the dye dilution method.

In this comparison the dye technique was the same as in the patients with acute myocardial infarction except that the dye here was injected into the pulmonary artery through a Cournand catheter No. 8 instead of a float catheter. This difference was evaluated by timing the duration of a 10 ml injection through the two catheters. The mean time of 10 measurements was 0.57 seconds, S.D = ±0.04 for one ml through the No. 8 catheter as compared to 0.66 seconds, S.D = ±0.07 for the PE 60 float catheter. Although this difference was significant ($P<0.01$) it is not thought to play an important role as the injection-time through the float catheter must be considered satisfactory.

The reproducibility of the dye technique with the Beckman cardiodensitometer was also tested by comparing duplicate investigations performed within 15 minutes in 6 consecutive subjects in regular sinus rhythm. The methodological error was 0.26 liters per min. These findings are illustrated in Fig. 5.

The stroke volume has been obtained by dividing the cardiac output by the heart rate obtained from the electrocardiogram. The cardiac index was calculated by dividing the cardiac output by the total body surface area obtained from a nomogram based on the formula of DuBois & DuBois (1916).

A point relevant to the present investigation which might distort the results is the monochromatic function of the Beckan Cardiodensitometer. This apparatus is equipped with only one filter system allowing for peak transmittance at a wavelength of 805 mμ which corresponds to the spectral absorptive maximum of the dye. It may therefore be possible that changes in haemotocrit affect readings. Changes in haematocrit may occur either over a longer period of time, or in the investigation involving cardiac output determinations before and after frusemide as described in Part III of this investigation. In this frusemide trial the maximum fall in cardiac output occurred at about one hour after its administration. The haematocrit was therefore taken before, and one hour after the administration of 40 mg frusemide in 6 patients with acute myocardial infarction. The overall change in haemotocrit was a increase of mean 2.3 per cent, ranging from 0 to 4 per cent for the group.

To evaluate the effects of a change in haematocrit multiple dye calibrations were performed on blood taken from 5 donors before and after plasma had

been siphoned off The haematocrit in each case was determined in duplicate in an Adams Autocrit Centrifuge (Clay-Adams Inc., New York) at 1.200 rpm for 5 minutes. The mean difference in heamatocrit was 7 0 per cent with a range from 3 to 11 per cent. These haematocrit changes were therefore considerably higher than the increases which followed the frusemide. In no instance was any significant alteration in dye calibrations seen. The mean calibration factor fell insignificantly from 1.24 to 1.20

COMMENTS

The validity of the dye dilution technique has been established in a series of studies showing satisfactory agreement when compared to Fick s method in human beings including both healthy volunteers and patients with cardiovascular disease (Hamilton et al. 1949 Werkö et al. 1949 Johnson 1951 Kopelman and Lee 1951 Doyle et al. 1953 Smith et al. 1954, Eliasch et al. 1955 Richardson et al. 1959 and Forsberg 1964)

As the present study involves patients with acute myocardial infarction there is a possibility that in the precence of severe cardiovascular failure estimates of cardiac output may be unsatisfactory even though no patients with shock were studied. Curves from patients in shock with peripheral injection of the dye have been critized by Orlol & McGregor (1967) who pointed to the dubious downslopes, obtained in these patients giving too large areas under the curve, and hence too low output values. These workers suggested either central injection of the dye as was always the case in the present study or the use of Dow s method of calculating the curve area (Dow 1955) as means of avoiding this source of error

STATISTICAL METHODS

Conventional methods have been used for the calculation of the arithmetic mean, standard deviation (S.D) and correlation coefficients (r)

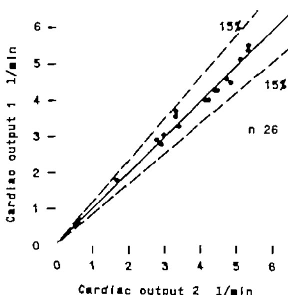


Fig 5 Plot of repeated cardiac output estimations performed within 15 minutes by the dye dilution method on 26 consecutive subjects in sinus rhythm. Lines indicate identity ± 15 per cent

Significance of differences between mean values were tested by Student s t test, and by ranking according to Wilcoxon when obvious non-normal distributions were seen (Scientific tables, Documenta Geigy 1962)

The Chi square test was used for testing the significance of differences of relative numbers. Yates correction was applied when small numbers were involved

Differences between correlations were tested according to Hald (1952)

Degrees of significance were tested at the 5 1 and 0 1 per cent level.

The error ratio was determined according to Simonson (1961) The methodological error obtained from duplicate estimations was calculated according to the formula $\sqrt{\frac{\Sigma d^2}{2n}}$ where d is the difference between the paired estimations and n the number of estimations.

Results

The results including relevant clinical data of the 50 cases of acute myocardial infarction are shown in *Table 11*. The table includes the pulmonary artery pressures obtained following the morning chest X-ray examination on the first day of hospitalization. In two patients (No. 41 and 43) a marked rise in pressures was subsequently recorded. Both were catheterized early in the course of their disease. No such pressure rise was observed in the other patients.

Fig. 6 shows the pressures obtained at pulmonary artery catheterization. With an upper normal limit for PAdp of 11 mmHg, raised pressures were initially present in 23 subjects (46 per cent). The mean PAdp for the whole group was 11.7 mmHg, S.D = ±5.0. The mean pulmonary artery pressure was 17.6 mmHg, S.D = ±6.0 and the mean systolic 27.0 mmHg, S.D = ±7.8.

No relationship between age and PAdp was found (r=0.06).

PAdp and infarction size and localization

As the maximum enzyme values are related to the size of the myocardial infarct (Kibe & Nilsson 1967 and Part I) a plot was made of PAdp pressures against maximum enzyme values (GOT) in those 47 instances where the patients survived long enough for maximum enzyme levels to be reached. The positive correlation (r=0.36, $P<0.001$) between PAdp and maximum GOT values is illustrated in Fig. 7.

Previous moderate hypertension, myocardial infarction and/or angina pectoris might increase the

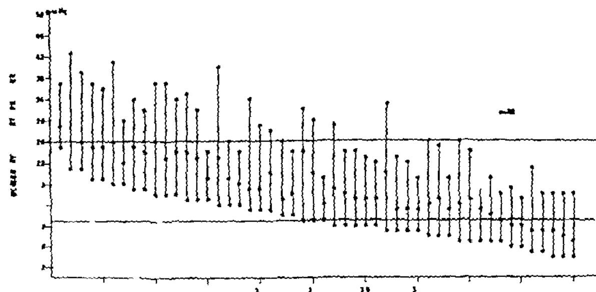


Fig. 6. Pulmonary artery pressures in 50 patients with acute myocardial infarction recorded on first morning after admission. Upper limit of normal (26 mmHg systolic, and 11 mmHg diastolic) are indicated by a horizontal line. Each vertical line indicates the pulse pressure and the mean pressure is indicated by the central dot.

mmHg
25 —
20 —
15 —
10 —
5 —

Pulmon ry artery diastolic pr ssure

n 47

550

20 60 100 140 180 220 260 300 340 380 420 460 500 units

GOT

Fig 7 Plot of pulmonary artery diastolic pressures and maximum GOT values in 47 patients with acute myocardial infarction

mmHg
25 —
20 —
15 —
10 —
5 —

Pulmonary artery diastolic pressure

n 26

20 60 100 140 180 220 260 300 340 380 units

GOT

Fig 8 Plot of pulmonary artery diastolic pressures and maximum GOT in 26 previously healthy patients with acute myocardial infarction.

TABLE 11 Clinical and laboratory findings including pulmonary artery pressure of the 30 patients investigated

Case	Age	Sex	Past history[1]	Delay (hours)	GOT max. (mU/ml)	ECG site of infarction	Signs of failure	PaO_2 (mmHg)	Heart rate (beats/min)	Respiratory rate/min	Pulmonary artery pressure (mmHg) Systolic	Diastolic	Mean	Infarction size at autopsy[2]
							At catheterization							
1	66	M	—	12	210	APL	R2	66	70	32	30	18	22	
2	69	M	—	3	99	A	R0	82	88	18	16	4	7	
3	55	F	—	23	74	A	R0	76	68	20	16	4	8	
4	60	F	H	29	290	A	R.,D	64	80	25	37	19	25	
5	58	M	—	8	(340)	A	R2	86	66	17	32	15	23	50R
6	47	M	—	25	350	A	R0	48	92	24	33	9	20	
7	67	F	IAHD	18	115	A	R3,D III	70	108	22	41	18	26	
8	66	M	A	16	172	P	R2	66	88	19	22	9	13	
9	71	M	A	30	260	A	R3,III	58	98	19	37	16	23	75
10	45	M	H	11	550	PL	R0	41	88	20	37	19	25	30
11	65	M	—	22	75	PL	R0	75	74	19	16	5	9	
12	64	M	H	28	290	PL	R2,III	75	64	22	40	14	23	
13	52	M	—	23	37	A	R1	68	74	18	19	8	13	
14	57	M	H	34	165	P	R0	73	66	16	30	11	20	
15	40	M	D	18	155	A	R1	71	82	20	26	14	19	
16	72	F	H	4	(40)	AL	R3,III	64	70	24	24	14	18	45R
17	48	M	—	30	85	A	R0	88	92	22	19	9	13	
18	57	F	—	14	92	L	R1,III	67	86	16	28	13	20	
19	58	M	A	56	170	AL	R1	66	92	30	22	10	15	
20	70	F	—	48	330	AL	R.	64	92	19	37	16	26	
21	47	M	—	7	250	AL	R1	58	86	18	24	7	15	
22	69	F	—	38	150	A	R0	76	94	22	16	7	11	
23	58	M	—	10	200	P	R1,III	82	66	16	24	12	16	
24	61	F	A	6	118	L	R2,III	78	60	20	32	11	22	
25	63	M	—	19	170	P	R0	104	54	17	23	9	15	25
26	58	M	—	18	62	P	R0	75	62	17	24	10	15	
27	58	M	I	24	137	P	R0	102	64	14	17	6	10	
28	71	F	A	19	161	P	R0	77	66	19	26	8	14	
29	61	F	AD	14	(81)	A	R4,D,III	47	114	28	37	25	29	70
30	74	F	AH	8	52	A	R0	74	104	18	21	5	9	
31	51	M	—	15	220	PL	R0	80	62	22	25	8	15	
32	54	M	—	15	280	A	R2	50	90	18	54	17	25	
33	57	M	AH	14	155	A	R1,III	75	66	15	29	10	17	

risk of latent heart failure. Therefore the 26 patients without such a history with available GOT maximum values, were separately studied with respect to the PAdp/maximum GOT correlation (Fig. 8). A weaker correlation was found (r=0.41 $P<0.05$) which does not significantly differ ($P>0.05$) from that of the 21 patients with a history of moderate hypertension, angina pectoris or myocardial infarction (r=0.72 $P<0.001$).

As regards the localization of the infarction the relationship between PAdp and available maximum GOT levels for the 24 patients with predominantly anterior infarcts (r=0.56, $P<0.01$) did not significantly differ from that for the 19 cases with predominantly posterior infarctions (r=0.77 $P<0.001$) (Fig. 9 and 10).

The association between the PAdp and the pathologist's estimate of infarction size expressed as a

Case	Age	Sex	Past history[1]	Delay (hours)[2]	GOT max. (units)[3]	ECG site of infarction[4]	Signs of failure[5]	At catheterization: PaO_2 (mmHg)	Heart rate (beats/min)	Respiratory rate/min	Pulmonary artery pressure (mmHg): Systolic	Diastolic	Mean	Infarction size at autopsy[6]
34	66	F	—	15	80	L	R2,III	66	102	20	34	16	24	
35	63	F	H	21	200	PL	R2	80	80	17	32	17	24	
36	49	M	IAH	21	310	P	R3,D,III	54	80	16	39	21	26	65
37	46	M	—	24	66	PL	R0	70	72	19	19	7	13	
38	72	M	IA	14	240	AL	R0	73	120	23	34	13	17	
39	78	M	—	14	55	A	R2	74	84	19	29	13	17	
40	63	M	A	8	280	PL	R1	81	70	22	26	12	15	
41	54	M	I	21	95	A	R1	71	84	17	15	6	10	
42	60	M	—	17	240	PL	R2,D	67	104	26	24	15	19	
43	61	M	—	6	240	A	R0	91	76	18	26	7	14	
44	62	M	—	28	104	P	R2	85	78	17	24	10	16	
45	68	M	—	4	270	AL	R0,III	79	60	15	23	10	15	
46	71	F	—	20	270	A	R2	44	86	25	35	15	24	35R
47	54	M	IAH	16	65	PL	R0	89	58	16	16	4	9	
48	76	F	A	18	80	A	R0	79	84	20	19	7	12	
49	62	M	A	9	240	A	R2,D,III	49	90	32	43	21	30	
50	43	M	—	24	130	PL	R0	58	76	17	19	11	14	

[1]) I =Infarction
A=Angina pectoris for more than one month before admission
H=Treated moderate hypertension
D=Diabetes mellitus

[2]) Delay=Interval between onset of symptoms and investigation

[3]) GOT in brackets refers to patients who died prior to GOT max. being available

[4]) A=Anterior
P=Posterior (inferior)
L=Lateral

[5]) Rales (R0, 1 ., 3 and 4) according to grading page 36
D=Dyspnoea
III=Third heart sound

[6]) Infarction size expressed in per cent of left ventricular myocardium
R=Rupture (All patients who died were autopsied)

per centage of the total left ventricular myocardium was also studied in the 8 subjects who died. The group is small and the relationship fell short of statistical significance (r=0.62 $P>0.05$)

PAdp and arterial oxygen tension

To reduce the possibility of hypoxia as a cause of pulmonary hypertension measurements of the pulmonary artery pressure were made with the patients receiving oxygen at a rate of 4 liters per minute when PaO_2 levels were normal or moderately reduced, i.e. $PaO_2 \geq 60$ mmHg, and 6 liters per minute when more severe degrees of arterial hypoxia were found PaO_2 levels in arterial blood were not checked routinely when the patients were on additional oxygen. However they were measured in 11 patients, 4 of whom had PaO_2 levels 47 to 54

Fig. 9 Plot of pulmonary artery diastolic pressures and maximum GOT values in 24 patients with predominantly anterior myocardial infarctions

Fig. 10 Plot of pulmonary artery diastolic pressures and maximum GOT values in 19 patients with predominantly posterior infarctions

mmHg on air In no case was the PaO_2 less than 75 mmHg with oxygen breathing

In an attempt to elucidate the effects of oxygen administration at rates of 6 liters per minute on patients with raised PAdp and arterial hypoxia two patients were investigated Their PAdp while breathing oxygen was 17 and 18 mmHg respectively With 6 liters oxygen per minute their PaO_2 increased from 50 and 66, to 80 and 134 mmHg respectively In the first patient the PAdp was first estimated with added oxygen, then without and finally again with oxygen. In the second patient the order was reversed, as shown in Fig. 11 Measurements were performed three times when the patient had been on, respectively off added oxygen for 30 minutes. In no instances was a change in PAdp of more than 2 mmHg obtained when changing between air and oxygen breathing In another 3 patients with PAdp within the normal range and PaO_2 66 to 77 mmHg the PAdp fell by one mmHg in one instance during oxygen breathing as opposed to air breathing.

Buscheman et al. (1967) noted a relationship between reduced cardiac performance, as estimated by the stroke volume, and PaO_2 in patients with acute myocardial infarction. A plot was therefore made of PAdp taken with the patients on their

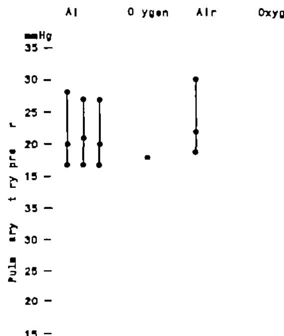


Fig 11 Pulmonary artery pressure levels in two patients during l and added oxygen breathing.

additional oxygen supplies against PaO_2 taken with the patients off their oxygen supplies. The negative correlation between these parameters is illustrated Fig. 12 ($r = -0.57$ $P < 0.001$)



Fig 12 Plot of pulmonary artery diastolic pressures and arterial oxygen tension in 50 patients with acute myocardial infarction.

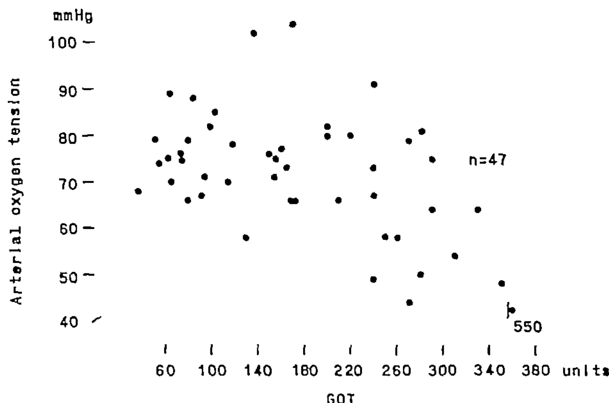


Fig. 13 Plot of arterial oxygen tension and maximum GOT values in 47 patients with acute myocardial infarction

A negative correlation was also found between GOT and PaO_2 as is shown in Fig. 13 ($r = -0.53$, $P < 0.001$). The correlation between PAdp and GOT has been shown previously (page 31). These correlations suggest that larger infarctions are accompanied by both reduced arterial oxygen tensions and increased PAdp. The relationship between PaO_2 and PAdp may be direct or indirect.

A similar association will be described on page 38 when the incidence and extent of rales are related to PaO_2 levels (Fig. 16).

PAdp and dyspnoea

The majority of patients had experienced some breathlessness during the early phases of their disease but only 6 were still dyspnoeic at the time of catheterization. Their mean PAdp (19.8 mmHg, S.D = ±3.4) was significantly higher when compared with that of the remaining 44 patients (10.5 mmHg, S.D = ±4.3) ($P < 0.001$).

PAdp and respiratory rate

Fig. 14 shows a plot of the respiratory rate taken immediately prior to catheterization (mean 20.1 per minute, S.D = ±4.2) and PAdp. A moderate correlation was found between these two parameters ($r = 0.44$, $P < 0.01$).

PAdp and rales

Rales as noted on auscultation in each subject prior to catheterization were graded

0 no rales
1 few scattered basal rales
2. bilateral basal rales extending to maximally one hand width up the chest
3 more than in 2 but not extending above lower half of the chest
4 more than in 3 but not heard all over the chest

Patients with more marked auscultation findings were never catheterized, as treatment could not be withheld.

mmHg

Pulmonary artery diastolic pressure

25 — 20 — 15 — 10 — 5 —

14 16 18 20 22 24 26 28 30 32

Respiratory rate

n 50

Fig 14 Plot of pulmonary diastolic pressure and respiratory rate in 50 patients with acute myocardial infarction.

The auscultation was performed by the investigator and a colleague was in each case asked to describe his findings for confirmation. Fig. 15 shows the relationship between PAdp and rales according to the above grading.

Rales grade 0 and 1 corresponded to normal mean PAdp of 8.1 mmHg, S.D = 3.8 mmHg and 10.0 mmHg, S.D = ±3.2 respectively. There was no significant difference when comparing the mean PAdp in these two groups ($P > 0.05$). In groups 2, 3 and 4 raised PAdp values were found with a combined mean of 15.9 mmHg, S.D = ±4.0 differing significantly from the combined mean PAdp in groups 0 and 1 which was 8.7 mmHg, S.D = ±3.7 ($P < 0.001$). No significant difference was found between the mean PAdp values of patients in group 2 and in group 3.

Of the 30 patients with rales grade 0 and 1, 24 had normal PAdp i.e. 11 mmHg or lower and 6 had raised PAdp which in one patient was marked (19 mmHg). Rales grade 2, 3 and 4 were heard in

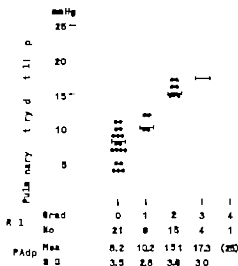


Fig 15 Pulmonary artery diastolic pressures for 50 patients with acute myocardial infarction grouped according to presence of pulmonary rales graded as given on page 36.

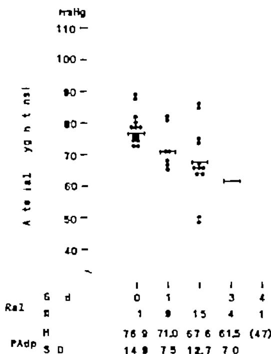


Fig. 16. Arterial oxygen tension in 50 patients with acute myocardial infarction grouped according to findings of pulmonary rales graded as given on page 36.

20 patients, and were associated with raised pressures in all but three.

Since the pressures in the pulmonary circulation may need to be elevated for a period of time before rales appear it is of interest to compare the delay time from the onset of acute symptoms to catheterization in the patients with grade 0 and 1 rales who had raised PAdp values, with that of those with grade 2. The former had a mean delay of 12 5 hours, S.D $= \pm 3\,6$ which did not differ from that of the latter whose mean was 18.9 hours, S.D $= \pm 10.8$ ($P > 0\,05$)

The described grading of rales in relation to arterial oxygen tension is illustrated in Fig. 16. If the PaO_2 values for group 0 and 1 mean 75 1 mmHg, S.D $= \pm 13\,3$ are compared with the PaO_2 in the subjects with rales grade 2 to 4, whose mean was 65 4 mmHg, S.D $= \pm 12\,3$ a significant difference is obtained ($P < 0.05$)

PAdp and a third heart sound

A third heart sound was heard in 13 subjects and their mean PAdp (15 5 mmHg, S.D $= \pm 4.7$) was significantly higher when compared to the mean PAdp (10.2 mmHg, S.D $= \pm 4.8$) of the remaining 37 patients without a third heart sound ($P < 0\,01$) The finding of a third heart sound was to a large extent parallel to the presence of rales. All patients with rales grade 3 and 4 had a third heart sound, and 4 of the 15 subjects with grade 2 rales also had a third heart sound, whereas in the subjects with no or an insignificant number of rales (grade 0 and 1) a third heart sound was heard in only 4 instances In these 4 patients the third heart sound was associated with a PAdp of 10 mmHg or more The highest PAdp in the absence of a third heart sound was 19 mmHg

PAdp and heart rate

The PAdp were plotted against heart rate in the 50 instances of acute myocardial infarction examined. A moderate correlation ($r = 0\,362$ $P < 0.01$) was found and is illustrated in Fig. 17

There was a fairly wide scatter and owing to the lower heart rate in patients with posterior infarctions a separate evaluation was made for these patients and compared with those having anterior or lateral infarcts.

A significantly higher mean heart rate was found in anterior and lateral infarcts, 86.3 beats per minute, S.D $= \pm 14\,9$ as compared with 72.2 beats per minute, S.D $= \pm 12.2$ for posterior infarcts ($P < 0\,01$) When plotting PAdp against heart rates in the former no clear correlation was found ($r = 0.32$, $P > 0.05$) In the case of posterior infarcts there was significant correlation between PAdp and heart rates ($r = 0\,53$ $P < 0.05$)

PAdp and pulse pressure

There was no apparent correlation between pulse pressures obtained by sphygmomanometer immediately prior to catheterization and the PAdp ($r = 0\,18$)

PAdp and chest X-ray

The chest X-rays were examined by two radiologists (Dr G Skogsberg and G Törnell, M.D) One examined the pictures twice The radiologists

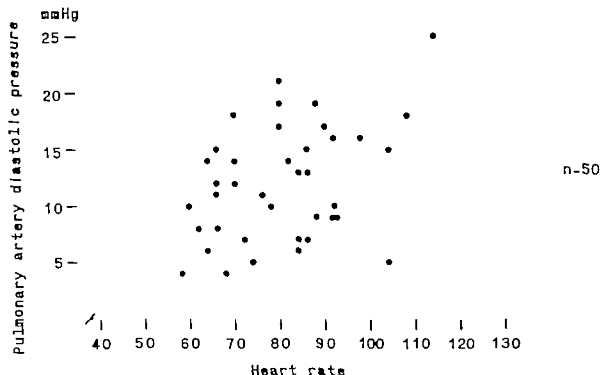


Fig 17 Plot of pulmonary diastolic pressures and heart rate in 50 patients with acute myocardial infarction.

were given no clinical or other information about the patients. The X rays were evaluated according to the following grading system.

0 No evidence of pulmonary congestion
1 Uncertain findings Possible evidence of pulmonary congestion
2. Central vascular enlargement
3 Peripheral vascular enlargement
4. Parenchymal infiltrations suggestive of pulmonary oedema, defined as confluent areas of varying severity and distribution

In addition a note was made on whether evidence of a pleural effusion was present, and on findings of localized upper lobe congestion. The findings are presented in Table 12.

Observer variation in chest X ray findings—The observer variation of one radiologist (Observer 1) was estimated by comparing his reports on all 50 chest X-rays made at two sessions spaced one week apart. The findings are shown in Table 12 It will be seen that 34 chest X rays were considered to be within normal limits at both sessions. Peripheral vascular enlargement was confirmed in 5 patients at both sessions one further patient being evaluated as doubtful in the second session. Similarly three episodes of radiological pulmonary oedema and two episodes of upper lobe congestion were found at both sessions. Only minor variations were noted in the reports made at the two sessions when patients with grade 0 1 and 2 X rays were considered. Of 12 X rays considered to show a pleural effusion at the first session this was confirmed in 10 at the second session.

Two main differences emerge if the reports of Observer 1 and 2 are compared. Observer 2 considered several chest X rays to show possible evidence of pulmonary congestion (grade 1) when Observer 1 reported these as normal. Observer 2 was also reluctant to regard central vascular congestion as an abnormal finding

Pulmonary artery diastolic pressure and chest X

TABLE 12 Chest X-ray findings of congestion and pleural effusion in relation to pulmonary artery diastolic pressures

			Observer 1				Observer 2	
			First session		Second session			
Case	PAdp (mmHg)	Delay (hours)	Congestion	Pleural effusion	Congestion	Pleural effusion	Congestion*	Pleural effusion
1	18	12	0	0	0	0	0	0
2	4	23	0	0	0	0	0	0
3	4	23	0	0	0	0	1	0
4	19	29	0	0	0	0	0	0
5	15	8	2	0	2	0	3	0
6	9	23	3	+	3	+	4	+
7	18	18	4	+	4	+	4	+
8	9	16	0	—	0	—	1	—
9	16	30	3	+	3	+	4	+
10	19	11	0	0	0	0	0	0
11	5	22	0	0	0	0	3	0
12	14	28	2	0	1	0	1	0
13	8	23	0	0	0	0	1	0
14	11	34	0	0	0	0	0	0
15	14	18	0	0	0	0	1	0
16	14	4	3	0	3	0	3	0
17	9	30	0	0	0	0	1	0
18	13	14	0	0	0	0	0	0
19	10	36	*l*	+	*ul*	+	*ul*	+
20	16	48	3	+	3	+	0	+
21	7	7	0	0	0	0	1	0
22	7	38	0	0	0	0	0	0
23	12	10	0	0	0	0	0	0
24	11	6	0	0	0	0	1	0
25	9	19	0	0	0	0	0	0

ay.—The results are shown in Fig. 18 for the reports made by Observer 1 (first session) and in Fig. 19 for those of Observer 2. Both show that the PAdp was raised in those patients with chest X rays which showed clear evidence of pulmonary congestion. The PAdp values in groups 2, 3 and 4 were significantly higher than those in groups 0 and 1 ($P<0.01$)

The PAdp was raised in several patients who according to both observers had normal chest X rays

Chest X ray evidence of failure may not appear until the pressures in the pulmonary circulation have been raised for a period of time Therefore the time interval between the onset of symptoms and catheterization was compared in those patients with a raised PAdp and X-ray evidence of left heart failure and those with raised PAdp and no evidence of failure. The mean delay from the onset of symptoms in the former group was 19.4 hours, S.D $= \pm 12.5$ and did not differ significantly from that of the latter group whose mean delay was 15.8 hours, S.D $= \pm 5.7$ ($P>0.05$)

In the 12 patients with evidence of pleural effusion (Observer 1 first session) 10 had associated pulmonary congestion. The mean PAdp in those 12 patients was 15.7 mmHg, S.D $= \pm 5.4$. Both radiologists reported localized upper lobe congestion in the same two patients who had normal PAdp values.

			Observer 1				Observer 2	
			First session		Second session			
Case	PAdp (mmHg)	Delay (hours)	Congestion*	Pleural effusion	Congestion*	Pleural effusion	Congestion	Pleural effusion
26	10	18	0	0	0	0	0	0
27	6	24	0	0	0	0	0	0
28	8	19	0	0	0	0	0	0
29	25	14	4	+	4	+	4	+
30	5	28	0	0	0	+	1	+
31	8	15	0	0	0	0	1	0
32	17	13	3	—	1	—	3	—
33	10	14	0	0	0	0	0	0
34	16	15	0	+	0	0	1	0
35	17	21	0	0	0	0	0	0
36	21	21	4	+	4	+	4	+
37	7	24	0	0	0	0	0	0
38	13	14	0	0	0	0	0	0
39	13	14	0	0	0	0	0	0
40	12	8	0	0	0	0	1	0
41	6	21	ul	+	ul	+	ul	+
42	15	17	1	+	1	0	3	0
43	7	6	0	0	0	0	0	0
44	10	28	0	0	0	0	0	0
45	10	4	1	0	0	0	1	0
46	15	20	2	+	1	+	1	0
47	4	16	0	0	0	0	0	0
48	7	18	0	0	0	0	0	0
49	21	9	3	+	3	+	1	0
50	11	24	0	0	0	0	0	0

) For grading see page 39 ul signifies upper lobe congestion

) 0 signifies no pleural effusion + signifies presence of pleural effusion — signifies inadequate X ray

Clinical and radiological findings indicating heart failure and PAdp

Table 13 gives a summary of clinical and radiological findings which were significantly related to PAdp The following findings were included A raised respiratory rate i.e. ≥23 (Altman et al. 1958) a heart rate ≥100, significant rales, i.e. grade 2, 3 and 4 according to the above criteria, the presence of third heart sound, dyspnoea and chest X ray findings considered as compatible with pulmonary congestion according to Observer 1 i.e. grade 2, 3 and 4 and pleural effusion. For purpose of evaluation of each clinical or radiological finding the error ratio is also included in the table showing that auscultation of the chest for rales seems to be the finding which most consistently reflects a raised PAdp Next in order of accuracy is the finding of pulmonary congestion on chest X ray examination

No combination of the different clinical signs or X-ray findings improved the accuracy in determining raised PAdp when compared to pulmonary auscultation for rales

Prognostic significance of raised PAdp

There was significant difference between the mean PAdp for those who subsequently died during the hospitalization (16.8 mmHg, S.D = ±4 9) and the survivors (10 7 mmHg, S.D = ±4.5) ($P<0$ 01) Of those with normal PAdp i.e. ≤11 mmHg, one patient out of 27 subsequently died as

TABLE 13 Pr al nc f lnu al finding l elation t p lmonary artery diastolic pressures

Pleural effusion							+											+		+						
Chest X ray grade —4																		+								
Dyspnoea																										
Third heart sound																						+		+		+
Rales grade —4																	+						+			+
Heart rate ≥100						+																				
Resp. rate ≥23																		+		+						
PA_{dp} (mmHg)	1	4	4	5	5	6	6	7	7	7	7	7	8	8	8	9	9	9	9	10	10	10	10	10	11	11

compared to 7 of the 23 subjects with raised PAdp ($P < 0.05$)

Of the 7 with raised PAdp who died, three died of left ventricular rupture and cardiac tamponade, 3 died in heart failure, and one in ventricular fibrillation due to reinfarction.

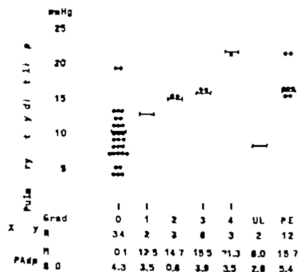


Fig 18 Pulmonary artery diastolic pressures for 50 patients with acute myocardial infarction grouped according to the chest X ray findings of Observer 1 UL signifies upper lobe congestion and PE the presence of pleural effusion.

Complications

Occasional ventricular ectopic beats and short runs of ventricular tachycardia occurred in some patients during the passage of the flow guided catheter through the right ventricle. They did not persist or require special treatment. In one patient, who was the last to be examined, a serious complication occurred when transient coarse ventricular fibrillation developed as the catheter was being manipulated in the right ventricle. It was initiated by an R on T ventricular ectopic beat and lasted for 21 seconds, ceasing spontaneously after the catheter had been withdrawn. This episode was associated with transient unconsciousness which lasted for approximately 15 seconds. The patient recovered rapidly and survived to leave hospital in good condition.

DISCUSSION

Pulmonary artery pressures during the acute stage of myocardial infarction were estimated in 50 patients. They were selected so that the haemodynamic findings observed were unlikely to be due to other cardiovascular diseases. Findings and conclusions are therefore valid only in this type of patient. No previous treatment for heart failure had been given and for obvious reasons the most sev

																								Error ratio
									+		+	+	+	+			+				+	+	+	0 52
						+		+		+	+	+	+		+		+				+	+	+	0 35
									+								+		+		+	+	+	0 52
	+		+			+		+				+		+			+				+	+	+	0 17
					+	+		+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	0 22
				+					+					+			+						+	0 61
				+				+	+		+							+	+		+		+	0 52
11	12	12	13	13	13	14	14	14	15	15	15	16	16	16	17	17	18	18	19	19	21	21	25	

erely ill, i.e. those patients with threatening or frank pulmonary oedema were excluded, as treatment had to be instituted before catheterization was possible.

Causes of raised pulmonary artery pressures

Several possible mechanisms may be involved in the production of raised pulmonary artery pressures after an acute myocardial infarction. These include a raised cardiac output, increased pulmonary vascular resistance and raised left ventricular filling pressures.

A raised cardiac output is an unlikely mechanism in the present context. Fluck et al. (1967) found low cardiac output values in patients with raised pulmonary artery pressures which is what might be expected if raised PAdp reflects failing left heart. Furthermore a good correlation between decreased cardiac output values and increased PAdp will subsequently be presented (page 48).

Increased pulmonary vascular resistance due to chronic pulmonary disease is also an unlikely cause in this study of raised pulmonary artery pressures as patients with cronic bronchitis and emphysema were excluded.

Severe hypoxia is known to increase pulmonary resistance (von Euler and Liljestrand 1946, Motley et al. 1947, Liljestrand 1948, Storstein 1952, Fritts et al. 1960 and Yu et al. 1963). According to Storstein (1952) raised pulmonary artery pressures will be seen when the arterial oxygen saturation falls to about 83 per cent which at normal pH

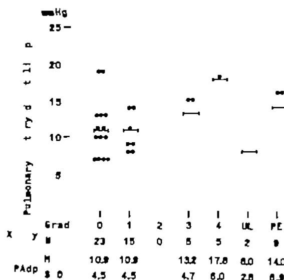


Fig. 19. Pulmonary artery diastolic pressure for 50 patients with acute myocardial infarction grouped according to the chest X-ray findings of Observer 2. UL signifies upper lobe congestion and PE the presence of pleural effusion.

values is equivalent to an arterial oxygen tension of about 45 to 50 mmHg. Such low values were rare among this group of patients, and the ad ministration of extra oxygen in a few patients did not have any appreciable effect on the PAdp. Still, added oxygen was given to the patients when the measurements used for evaluation were obtained

In acute myocardial infarction the most likely cause for the raised PAdp is an elevated left ventri cular filling pressure. A raised left ventricular end diastolic pressure in both experimental myocardial infarction, as well as in man has been found by Kirby et al. (1968) Nixon et al. (1968) Cohn et al. (1969) Hodges et al. (1969) and Hood et al. (1969)

Other possible changes which may account for the raised pulmonary artery pressures must also be considered. Increased levels of adrenaline and nor adrenaline after acute myocardial infarction ha e been demonstrated by several workers (Forssman 1954, Valori et al. 1967 Wallace 1968 and Mc Donald et al. 1969) Gazes et al. (1959) found levels of noradrenaline to be related to transaminase levels and Jewitt et al. (1969) found notably high levels of free adrenaline and noradrenaline in the urine of those patients who devloped heart failure and shock.

Since Johansson & Lindell (1970) have recently shown that the pulmonary artery pressure rises during catecholamine infusions given to pa tients with chronic atrioventricular block and fixed rate artifical pacemakers, the increased sympatho-adrenal discharge seen in patients with infarction may be a factor The mechanism of this change in pulmonary artery pressure requires further study in animals with experimental infarction since it may involve a direct action on the pulmonary vascular bed or an increase in systemic after load with resulting elevation of left ventricular filling pressures.

Relationship between PAdp and some relevant variables

I farction size

A significant correlation between PAdp and in farction size as estimated by maximum GOT values was found A relationship between enzyme levels and size of myocardial infarction as estimated at autopsy has previously been described by Kibe and Nilsson (1967) and was confirmed in Part I of this study This finding is in agreement with a similar relationship between size of experimentally induced infarcts and the rise in left ventricular end-diastolic pressure demonstrated by Hood et al. (1967)

The correlation found between increasing PAdp with increasing infarction size is parallel to the finding of a raised incidence of larger infarcts in patients with clinical signs of left heart failure in previously compensated patients described in Part I of this study

Arterial oxygen tension

A significant negative correlation was found between arterial oxygen tension and PAdp levels. Blood gas disturbances associated with myocardial infarction have been studied by several investigators (MacKenzie et al. 1964, McNicol et al. 1965 Valentine et al. 1966, Buschman et al. 1967 Ljungström et al. 1967 Shap ro et al. 1968, Storstein & Rasmussen 1968 and Sukumalchantra et al. 1969) A high incidence of arterial hypoxaemia with normal or slightly lowered carbon dioxide tensions has been the usual finding The three pathophysiological mechanisms discussed are veno-arterial shunting in the lungs, uneven ventilation-perfusion ratios and possibly even diffusion defects.

Although these authors found lower PaO_2 values in patients with infarction complicated by pulmonary congestion, McNicol and co-workers (1965) did not find a clear association between physical signs of pulmonary congestion, i.e. pul monary rales, and arterial oxygen tension Most of the above workers agree that the severity of hy poxaemia is greater in patients with a clinically more severe illness. In addition Buschman et al. (1967) have demonstrated a correlation between the degree of arterial hypoxaemia and the reduction in stroke volume.

An association between the clinical assessment of heart failure and degree of hypoxaemia was also

found in the present study. Patients with more than a few scattered basal rales had a significantly lower mean arterial oxygen tension than those without. On the other hand the author agrees with McNicol et al. (1965) that fairly severe hypoxia is at times found in subjects with practically normal pulmonary auscultatory findings. Another reported discrepancy between e.g. radiological findings of failure and arterial hypoxaemia in acute myocardial infarction is that while the former resolves within a few days the hypoxaemia commonly persists for a considerably longer period (Valentine et al. 1966).

Clinical findings of left heart failure

The incidence of pulmonary congestion as estimated by the degree of rales was found to be well related to raised PAdp and the presence of more than a few scattered basal rales would seem to indicate the presence of raised PAdp with fair accuracy. This was the case in 17 instances of 20 with these clinical findings. Of the 27 patients with normal pulmonary artery pressures only 3 had significant basal rales. In one patient (No. 10) normal physical findings were associated with a considerably raised PAdp (19 mmHg) and in this patient significant rales developed only on the fifth day of hospitalization. Little is known about the time relationship between the haemodynamic changes and clinical findings in myocardial infarction. Animal experiments would suggest that altered pressure patterns are found extremely early after coronary occlusion (Hood et al. 1969). In the present study two instances were met in which clear increases occured in the PAdp within two hours of catheterization (cases No. 40 and 43). Both patients were investigated early, i.e. 8 and 6 hours from onset of symptoms respectively. In one (No. 43) pressures rose from 7 to 15 mmHg and rales, previously absent, were heard within one hour of this pressure-rise. Similarly an increase in rales was also found in patient No. 40 whose PAdp rose from 12 to 16 mmHg. In neither of these instances did the patient mention retrosternal pain during the period of observation, suggesting further extension of the infarct.

Chest X-ray

The main conclusion to be drawn from the chest X ray study is that although findings indicative of pulmonary congestion were associated with raised PAdp, several patients with raised pressures were found to have normal chest X-rays. A shorter time interval from onset of symptoms to examination was not the explanation for this descrepancy.

In the present material there were only two patients with X ray signs of localized upper lobe congestive changes as reported by Meltzer (1968) and Tattersfield et al. (1969). The PAdp was normal in both.

Since this finding was rare in the present study when compared to the incidence of 76 per cent in the investigation of Tattersfield et al. few conclusions can be drawn. This difference may depend on different patient postures. In the CCU of Serafimerlasarettet patients are usually nursed in a propped up position. Hypotension would naturally influence the positioning of these patients but this was present in neither of the patients with upper lobe congestive changes. The present findings are in agreement with those of Fluck et al. (1967) who reported high pulmonary artery pressures in association with radiological oedema but they also had some patients with raised pulmonary artery pressures and no radiological evidence of pulmonary oedema.

Value of pulmonary artery catheterization in acute myocardial infarction

The value of these studies has to be weighed against the risks of inflicting harm on the patients. The increased mortality in patients with left heart failure described in Part I indicates that a better understanding of the different aspects of this complication of an acute myocardial infarction as well as improved knowledge of the therapeutic effects of drugs employed (see Part III) is essential. It was therefore felt that flow guided pulmonary artery catheterization was justified in these patients. Furthermore the procedure had been found safe in other reported studies. Adequate facilities for the management of ventricular arrhythmias, should they occur, were always within easy reach.

An important question is whether the inclusion of pulmonary artery pressure recordings in the routine care of patients with acute myocardial infarction could be replaced by a simpler and completely risk free method. It is simpler to measure the central venous pressure, but this need not give any information as to the changes in the left heart which is primarily affected in acute myocardial infarction. Indeed, a poor relationship between changes in central venous and pulmonary artery diastolic pressures has been demonstrated by Rapaport & Scheinman (1969).

As would be anticipated with a measurement which provides an important guide to left ventricular filling pressures the PAdp in this study correlated well with more crude clinical parameters of heart failure. These findings are indicated in Table 13 in which it is seen that the best agreement found was between the extent of pulmonary rales on auscultation and the level of PAdp. The relationship between the extent of pulmonary congestion on the chest X ray and the PAdp was slightly less satisfactory.

The pulmonary artery pressures obtained in this study therefore provide a clear basis for the assessment of therapeutic regimes. At present it is not wise to recommend the general use of this technique in routine coronary care units since the value would not always be utilized. Instead the method is best used in units with a committment to evaluate new and old treatment regimes in e.g. cardiovascular failure in addition to routine patient care.

Pulmonary artery catheterization also provides an objective parameter of prognostic value. Of the 27 patients with normal PAdp only one died during his hospital stay whereas 7 died of those 23 patients with initially raised PAdp. However, no indication of mode of death is obtained, which is in accordance with the findings based on a clinical diagnosis of heart failure and mode of death in myocardial infarction (Norris et al. 1968). As to the relationship between a raised pulmonary artery pressure and prognosis Fluck and co-workers (1967) did not show any significant difference amongst those with raised pressures compared with those with normal pressures. There was a tendency however to a poor prognosis associated with pulmonary artery hypertension as 5 of their 21 subjects with raised pressures died whereas the 6 with normal pressures survived.

Fluck et al. (1967) investigated right heart pressures in 27 consecutive episodes of acute myocardial infarction in 26 patients. Their study differs from the present investigation in that there was no negative selection of patients with a history of heart failure, treated or untreated, pulmonary disease and valvular heart disease. One patient with mitral incompetence was included and two had chronic bronchitis. These authors use the pulmonary artery systolic pressure for evaluation of their findings as opposed to the diastolic pressure in the present study. On the other hand a basis for comparison remains as the correlation between systolic and diastolic pressures in the pulmonary artery is good. It was found to be highly significant in the present investigation ($r = 0.85, P < 0.001$). In addition, and for comparative purposes, the relationship between PAdp and mean pressure was also highly significant ($r = 0.94$, $P < 0.001$).

Fluck and co-workers (1967) found that 80 per cent of their patients had pulmonary artery hypertension as compared with 46 per cent in the present study. Several factors may have contributed to the high figures of Fluck et al.: patient selection as well as examination position. Most of their patients were in the supine position and this is known to increase pressures in the lesser circulation (Lagerlöf et al. 1951 and Eliasch et al. 1961). This observation has also been reported more recently in patients with acute myocardial infarction (Eddy & Singh 1969).

SUMMARY

The pulmonary artery diastolic pressure may reflect the left ventricular filling pressure. It has thus been determined in 50 episodes of acute myocardial infarction in 49 subjects. The patients have been selected to provide a group where the acute infarct was in all probability the main cause of the

haemodynamic findings The initial PAdp in 23 patients (46 per cent) were above the upper limit of normal

The pulmonary artery diastolic pressures have been compared to clinical, radiological and laboratory findings. A moderate correlation between an elevated PAdp and infarct size as estimated by GOT maximum values was found. A negativ correlation was found between PAdp and arterial oxygen tension and also between GOT and PaO_2 A poor prognosis is associated with raised PAdp The PAdp level was related to several clinical parameters and the presence of pulmonary rales on auscultation provides the most accurate clinical sign of a raised pressure in the lesser circulation.

Flow guided catheterization of the pulmonary artery at the bedside did not disturb the patients and is usually completed in a short time. It is associated with a small risk of incl ding ventricular arrhythmias

B. CARDIAC OUTPUT AND STROKE VOLUME IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

MATERIAL AND METHODS

The methods have been accounted for Cardiac output estimations were performed at least twice within the space of one hour In two it was only obtained once owing to technical difficulties. The mean of the results obtained were used in the present investigation.

The patients constitute 18 of those 50 accounted for previously (page 32) who were subjected to pulmonary artery catheterization. The group investigated is highly selected It consists in part of patients with raised PAdp who took part in the drug trial presented in Part III, and for purpose of comparison also patients with PAdp within the normal range.

The patients were studied on the first day of hospitalization. In 10 subjects this was during the first 24 hours from onset of symptoms which led to admission, and in the remaining 8 within 48 hours. In all the diagnosis was confirmed by characteristic electrocardiographic and serum enzyme changes, and in the 4 who subsequently died by post mortem examination as well.

There were 13 men and 5 women aged 45 to 71 with a mean of 59 years. Eleven patients had basal rales (grade 2 to 4) a few scattered basal rales were heard in a further 2 whereas normal pulmonary auscultatory findings were present in 5 patients In 10 patients a third heart sound was heard and 7 patients had radiological signs of pulmonary congestion.

The data on these patients including clinical findings enzyme values and haemodynamic results are shown in Table 14, which includes the PAdp at time of the cardiac output determinations.

Results

Relationship between GOT and cardiac output and stroke volumes

No significant correlation was found between maximum GOT values and the cardiac output in this group (r=—0.25) Nor was a significant relationship obtained when performing a similar comparison between GOT and stroke volumes (r= —0 16) The relationship between GOT and PAdp in these patients also fell short of statistical significance (r=0 45 $P>0\,05$)

PAdp and cardiac output

Five of the patients had PAdp values within the normal range, whereas raised pressures were present in the remaining 13 A significant negative correlation was obtained when plotting PAdp against cardiac output (Fig. 20) (r=—0 73) $P<0.001$) The mean cardiac output for those 5 subjects with PAdp within the normal range was 5.8 liters per min S.D = ±1 1 and this was significantly higher when compared with the mean cardiac output in those with raised PAdp values, 3 9 *liters per min.*, S.D = ±1 0 ($P<0\,01$) Adjustment for body surface area did not appreciably affect the findings.

PAdp and stroke volume

Similarly the subjects with normal PAdp had significantly higher stroke volumes (mean 70.8 ml, S D = ±10 5) as compared to those with raised PAdp (mean 48.3 ml, S D = ±17 1) ($P<0.05$) A significant negative correlation was obtained between PAdp and stroke volume (r= —0 72 ($P<0\,001$)

TABLE 14 Salient [illegible] of the 18 patients in whom cardiac output determ[illegible] were performed

Case	Age	Sex	Body surface area (m^2)	ECG site of infarction	GOT max. (units)	Day[b]	Oral temp. (C)	Third heart sound	Rales	Blood pressure (mmHg)	Chest X ray[e]	PaO_2 (mmHg)	PAdp (mmHg)	Cardiac output l/min.	Stroke volume (ml)	Fate
4	60	F	1 77	anterior	290	2	37 3	0	2	130/90	0	64	19	4 5	56	survived
6	47	M	1 93	anterior	330	2	36.8	0	0	135/90	3	48	9	5 4	54	survived
7	67	F	1 69	anterior	115	1	36 9	+	3	165/78[d]	4	70	18	4.5	43	survi ed
9	71	M	1 77	anterior	260	2	37 4	+	3	141/82[d]	3	58	19	2 8	55	died
10	45	M	1 89	posterolateral	330	1	37 3	0	0	124/87[d]	0	41	17	4 0	49	died
11	65	M	2 00	posterolateral	75	2	38 0	0	0	120/85	0	75	5	5 8	72	survived
12	64	M	1 86	posterolateral	290	2	37 4	+	2	103/57[d]	2	75	16	6 1	86	survived
23	58	M	2 18	posterior	200	1	37 4	+	1	145/95	0	82	12	3 4	57	survived
4	61	F	1 63	lateral	118	1	36 9	+	2	172/84[d]	0	78	12	3.6	58	survived
[illegible]9	61	F	1 54	anterior		1	38 0	+	4	101/72[d]	4	47	23	1 8	16	died
34	66	F	1 64	lateral	80	1	36 3	+	2	130/85	0	66	16	3 6	57	survived
36	49	M	1 70	posterior	510	2	37 4	+	3	133/97[d]	4	54	17	5 4	33	died
37	46	M	2 17	posterolateral	66	2	36 0	0	0	130/90	0	70	7	5 4	70	survived
40	63	M	1 98	posterolateral	280	1	36 6	0	2	173/93	(0)	81	16	4.1	60	survived
41	54	M	1 67	anterior	95	2	37 6	0	1	140/80	nl	71	6	7 6	76	survived
43	61	M	1 80	anterior	40	1	36 6	0	2	150/88[d]	(0)	91	15	4 8	57	survived
45	68	M	1 93	anterolateral	270	1	36 4	+	0	130/95	1	79	10	4.7	82	survived
49	62	M	1 92	anterior	240	1	—	+	2	174/89[d]	3	49	19	3 5	41	survived

) GOT maximum when the patient survived long enough for this to be obtained
) day after onset of symptoms which led to admission
) rales graded as on page 36
) denotes intraarterial measurement
) chest X ray grades, as on page 39 Figures in brackets refer to findings at time of considerably lower PAdp
[f]) PAdp at time of measurement of cardiac output

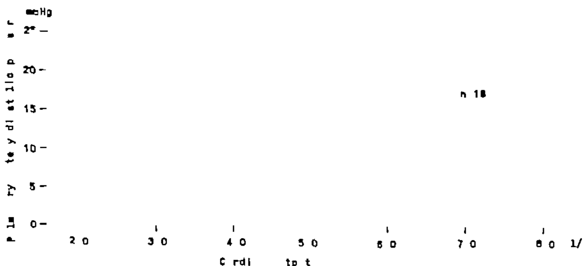


Fig 20 Plot of pulmonary artery diastolic pressures and cardiac output in 18 patients with acute myocardial infarction

Relationship between cardiac output and stroke volume with clinical and radiological signs of left heart failure

The mean cardiac output for the 7 patients with practically normal pulmonary auscultatory findings (grade 0 and 1 see page 36) was 5.2 liters per min., S.D = ±1 4 and differed significantly from the mean of 3 9 liters per min., S.D = ±1 1 in those with rales grade 2, 3 and 4 ($P<0.05$) Similarly when the stroke volume for these two groups is compared, a *significant difference was found* Those with failure according to these criteria had a lower mean stroke volume (47.5 ml, S.D = ±18.6) than those with no failure (mean 65 7 ml. S.D = ±12.4) ($P<0.05$)

The mean cardiac output for the 7 patients with chest X ray findings of left heart failure (grade 2, 3 and 4) was 3 9 liters per min., S.D = ±1 5 which did not differ significantly from a mean of 4.7 liters per min., S.D = ±1.2 in the 11 patients with no clear radiological signs of failure, or upper lobe congestion only ($P>0.05$) Similarly the mean stroke volumes in these two groups of 44.0 ml, S.D = ±21.8 and 61.3 ml S.D = ±12 9 respectively did not differ significantly ($P>0\ 05$)

Cardiac output and stroke volume in relation to prognosis

The mean cardiac output for the survivors was 4.8 liters per min S D = ±1 2, which differed significantly from a mean of 3 0 liters per min., S.D = ±0 9 in those who subsequently died ($P<0\ 05$) Similarly the mean stroke volume in those who survived (60 6 ml. S.D = ±15.0) was higher than that in those who died (33 3 ml. S.D = ±13 5) ($P<0\ 01$)

Stroke volume and arterial oxygen tension

The relationship between stroke volume and arterial oxygen tension is illustrated in Fig 21 A significant correlation was found (r=0 60 $P<0.01$) The corresponding findings for the cardiac output was r=0 35 ($P>0\ 05$)

Complications

No complications were encountered in 17 patients. The arterial line formed a knot and could not be withdrawn by traction in one patient. It had to be removed through a small incision in the right femoral artery under local anaesthesia. No symptoms suggestive of arterial obstruction resulted and oscillometric investigation prior to discharge from hospital revealed entirely normal findings.

DISCUSSION

The cardiac output, stroke volume and PAdp were measured in 18 subjects with acute myocardial infarction. A correlation between raised PAdp and

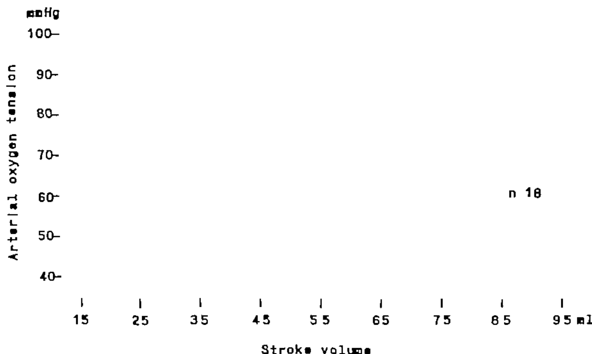


Fig 21 Plot of arterial oxygen tension and stroke volume in 18 patients with acute myocardial infarction

low cardiac output and stroke volume was found. Furthermore it was seen that like raised PAdp levels low cardiac outputs and stroke volumes indicated poor prognosis. Patients with clinical signs of failure in the form of pulmonary rales were found to have significantly lower cardiac output and stroke volume values than those without these findings. On the other hand no such difference was found when the same comparison was performed based on radiological evidence of left heart failure. Recently Buschman and co-workers (1967) demonstrated a relationship between PaO_2 levels and stroke volume in patients with acute myocardial infarction. This association was confirmed in the present investigation.

The present investigation was performed with the patients ecerving added oxygen given in the humidified form at a rate of 4 to 6 liters per min. Mac Kenzie et al. (1964) Thomas et al. (1965 b) Cameron et al. (1966) and Buschman et al. (1967) have shown that in patients with acute myocardial infarction added oxygen will raise the systemic vascular resistance and the arterial blood pressure while lowering the cardiac output and stroke volume. In contrast an increase in cardiac output in patients with more severe degrees of hypoxaemia was found by Sukumalchantra et al. (1969) The heart rate is generally not significantly altered. The results presented may therefore be affected accordingly

A varying incidence of low cardiac outputs in patients with acute myocardial infarction has long been recognized. Among the earliest observations are those of Gruhman & Master (1941) and Starr & Wood (1943) With the introduction of the Fick, dye and radioisotope dilution methods these findings have been confirmed (Pritchard & Hellerstein 1950 Gilbert et al. 1951 Freis et al. 1952, Gilbert et al. 1954, Smith et al. 1954, Gammill et al. 1955 Gunton et al. 1957 Lee 1957 Broch et al. 1959 Murphy et al. 1963 MacKenzie et al. 1964 and Ramo et al 1969) Furthermore a elationship between severely affected haemodynamics and prognosis has been shown by some of the above mentioned authors. This finding was not confirmed by Malmcrona & Varnauskas (1964) but their patient group did not contai patients in shock or severe heart failure.

More recently significant contributions have been made on the course of haemodynamic changes for varying lengths of time after the acute event by Malmcrona (1964) Thomas et al. (1965 a) and Nager et al. (1967) The former also pointed to the fall in peripheral resistance but not in cardiac output in the subjects with more marked temperature reactions

In the present group of patients, lower output values were found in patients with clinical heart failure. Low cardiac output values in patients with acute myocardial infarction with signs of left heart failure have previously been found by Freis et al. (1952) Gilbert et al. (1954) Gammill et al. (1955) and Lee (1957) The latter compared the cardiac output of patients with acute myocardial infarction with those obtained in a group of patients with left ventricular failure due to other aetiologies. In no instance was the cardiac output as low in patients with acute myocardial infarction and signs of left heart failure as that observed in patients with left ventricular failure due to other causes.

The majority of the above authors noted a relationship between the severity of the clinical picture and cardiac output reduction which was particularly marked in the patients in shock and heart failure. On the other hand several earlier investigators using dye-dilution curves injected the dye into a peripheral vein and may therefore have erroneously low cardiac output values in the most severely ill patients (Orrol & MacGregor 1967)

The observation in this study that an elevated PAdp level was correlated with a low cardiac output and stroke volume after acute myocardial infarction, is important, as this indicates that these patients were performing on a depressed left ventricular function curve. These measurements provide a clear basis for the subsequent investigation of an inotropic agent and a diuretic, since with the former, improvement in the function of the ventricle should be apparent at the same, or reduced, left ventricular filling pressure. In the case of a diuretic it is important to check that as a result of fluid loss, and subsequent hypovolaemia, there is no gross reduction in left ventricular performance due to a reduction in left ventricular filling pressures.

SUMMARY

In 18 patients with acute myocardial infarction examined on the first or second day of their illness a good relationship has been demonstrated between a decreased cardiac output and stroke volume, and a raised PAdp Furthermore, significantly lower stroke volumes were found in those with clinical signs of left heart failure, as was the case with the cardiac output measurements Both a low cardiac output and a low stroke volume indicated a poor prognosis.

PART III

THE EARLY HAEMODYNAMIC EFFECTS OF OUABAIN AND FRUSEMIDE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND RAISED PULMONARY ARTERY DIASTOLIC PRESSURES

Salutary effects of digitalis in acute myocardial infarction were described as early as 1912 by Herrick in his classical paper Since then diverse opinions have been forwarded and uncertainty as to whether digitalis exerts a positive inotropic effect in these patients remains. In several reports the early haemodynamic effects of digitalis in chronic heart failure have been described but only two had been performed in patients with acute myocardial infarction when this study was started. The first was performed by Malmcrona and co-workers in 1966, who reported on 10 patients, none of whom were in left ventricular failure. More recently Balcon et al. (1968) presented results obtained in 11 subjects who showed signs of early left ventricular failure.

Although diuretics are frequently used in the management of the heart failure seen in acute myocardial infarction, no study seems to have been published to date on the haemodynamic effects which follow the administration of these drugs in this condition.

The present investigation is concerned with the early haemodynamic effects of ouabain and frusemide in patients with acute myocardial infarction who were found to have raised pulmonary artery diastolic pressure (PAdp)

MATERIAL AND METHODS

In this trial ouabain 0 75 mg and frusemid (Lasix®) 40 mg were both given in a single dose The methods for obtaining the various haemodynamic parameters have been described previously on pages 24 to 29

The *systemic resistance* was calculated according to the formula

$$\frac{\text{mean aortic pressure} \times 1332}{\text{cardiac output in ml/sec.}} \quad \text{dyn.sec.cm}^{-5}$$

The right atrial mean pressure was not taken into account.

Left ventricular minute work was expressed in kilogrammeters per minute and calculated according to the formula

$$\frac{\text{cardiac output} \times (\text{mean aortic pressure} - \text{PAdp}) \times 13\ 6}{1000}$$

The *left ventricular stroke work* was expressed in grammeters. It was obtained by the same formula but with stroke volume substituting the cardiac output.

Statistical methods

Conventional methods have been used for the calculation of the arithmetic mean, standard deviation (S.D) and correlation coefficients (r) Significance of differences between mean values were tested by Student's t-test. The Chi-square test was used for testing the significance of differences of relative numbers. Yates correction was applied when small numbers were involved

Degrees of significance were tested at the 5 1 and 0 1 per cent level.

Procedure

The patients were examined propped up in bed at approximately 30° They were given oxygen continuously at a rate of 4 or 6 liters per minute. Drugs known to affect the haemodynamic state were not

TABLE 15 Salient features of the 9 patients included in the ouabain and frusemide trial

Case	Age	Sex	ECG site of infarction	GOT max. (Units)	Day	PaO_2 (mmHg)	Rales	Third heart sound	Chest X ray	Order of trial	Infarction size at autopsy*
12	64	M	posterolateral	790		75	2	+	2	frusemide/ouabain	Survived
10	45	M	posterolateral	550	1	41	0/1	0	0	ouabain/frusemide	30
13	61	M	anterior	240	1	91	2	0	(0)	frusemide/—	Survived
9	71	M	anterior	60	2	58	3	+	3	ouabain/frusemide	75
46	49	M	posterior	310	2	54	3	+	4	frusemide/ouabain	65
49	62	M	anterior	40	1	49	2	+	3	ouabain/frusemide	Survived
40	63	M	posterolateral	280	1	81	2	0	(0)	frusemide/—	Survived
29	61	F	anterior	81	1	47	4	+	4	ouabain/—	70
7	67	F	anterior	115	1	70	3	+	4	frusemide/—	Survived

) GOT value not representing maximum owing to early death of the patient.) Day after onset of symptoms which led to admission. *) Rales graded 0 to 4 as described on page 36.) Chest X ray grading as described on page 39. Figures in brackets refer to findings at time of considerably lower PA_{dp}.) Size of infarction expressed in per cent of the left ventricular myocardium as found on autopsy

given. Blood withdrawn when recording dye curves was reinjected to keep blood volume reasonably constant.

In the present study pulmonary artery pressures, aortic pressures, and the heart rate were determined every 15th minute for one hour which gives a control period. The cardiac output, stroke volume, systemic resistance, left ventricular work and left ventricular stroke work were obtained at least 3 times within this period. 0.75 mg ouabain or 40 mg frusemide in 10 ml saline was then slowly injected through the pulmonary artery float catheter and the same variables were then again measured every 15th minute during the following two hours. For evaluation the mean values of the control hour were compared with the mean of successive one hour periods starting 15, 30, 45 and 60 minutes after the injection of the drug. Alternate patient in this trial received frusemide first, the others ouabain. A 4 hour rest was interposed between the two drugs trials in the 5 patients who received both ouabain and frusemide.

Patient material

The patients included in this study were those presented in Part II who had an elevated PAdp of 15 mmHg or more, and were thus considered to have haemodynamic evidence of left ventricular failure with the acute infarction as its main cause. If a patient had passed through the first drug trial and still had a raised PAdp, i.e. 12 mmHg or more, they were included in the haemodynamic evaluation of the other drug.

All patients whose PAdp was elevated were not studied as in some clinical deterioration required urgent treatment. These included patients who developed AV block or recurrent and severe chest pain. Two patients under consideration for the study collapsed with cardiac tamponade due to left ventricular rupture.

Nine patients remained for the present study and details of the salient clinical and laboratory findings are given in Table 15. Four of these 9 patients died during hospitalization. Further details of these patients are given below.

Case 9. 71 year old man with history of angina pectoris. Anterior infarct, GOT 260. Investigated on second day of his illness. He developed increasingly severe arterial hypoxia and failure and was therefore placed on respirator on the 8th day in hospital but died in ventricular fibrillation on the 9th day. Autopsy revealed that 75 per cent of the left ventricular myocardium was infarcted.

Case 10. 45 year old man. Previous moderate hypertension treated sporadically. Posterolateral infarct, GOT 550. Investigated on first day of his illness. The patient developed AV-block III on the 3rd day in hospital and was treated with endocardial pacing until normal sinus

rhythm had been restored He died 21 days after admission in ventricular fibrillation due to reinfarction. The original infarct involved 30 per cent of the left ventricular myocardium.

Case 29 61 year old woman with history of angina and diabetes Anterior infarct. Investigated on first day *of her illness Subjective symptoms were mild in comparison* to clinically severe left heart failure. Fou hours after the ouabain trial the patient suddenly became restless and more dyspnoic. She could therefore not be further investigated and was immediately given frusemide. A diuresis started but he died 1 1/2 hours later in frank pulmonary oedema and asystole. Post mortem examination revealed that 70 per cent of the left ventricular myocardium was infarcted.

Cas 36. 49 year old man with previous moderate hypertension, angina and one infarction. Posterior infarct, GOT 310 Investigated on second day of his illness. Although responding haemodynamically to treatment this patient developed progressively more severe heart failure and hypotension He died in pulmonary oedema on the *5th day in hospital. Autopsy showed that 65 per cent of* the left entricula myocardium had been recently infarcted. There was also further small old infarct giving total infarcted area of about 70 per cent

In the following the results obtained in the ouabain trial will be presented first, followed by a discussion, and thereafter the frusemide trial

Patients

Five men and one woman were investigated. The salient features of these patients are given in Table 15 Their mean age was 59 years with a range of 45 to 71 The diagnosis was confirmed in all by a characteristic enzyme rise and an electrocardiographic pattern of a transmural infarction. All patients showed clinical and radiological signs of left heart failure, except one patient (No. 10) who only later in the course of his illness developed moderate basal rales The patients were investigated in the course of the first day in hospital, which in 3 was equivalent to the first day of the illness and in the remaining 3 to the second day Two had previously taken part in the frusemide trial.

Results

The results for each patient are given in Table A of the Appendix. A summary of significant alterations found following ouabain is given in Table 16 The haemodynamic characteristics obtained from the mean values during the control period of the patients investigated were as follows. Mean PAdp was 17 9 mmHg, S.D = ±3.6 The mean cardiac output was 3 8 l ters per min., S.D = ±1 5 and the mean stroke volume 45 ml. S.D = ±24. The mean heart rate was 86.9 beats per min., S.D = ±6 7

Heart ate

If the mean control value for the group is compared with the mean from the last 5 estimations there was an insignificant fall from 86.9 beats per min., S.D = ±6 7 to 84 9 beats per min., S.D = 12 0 ($P>0.05$) A rise in heart rate of 3 4 beats per minute was found in one patient which was significant (No. 12, $P<0\ 01$) a significant fall in two (No. 29 $P<0.001$ and No 49 $P<0\ 05$) whereas no change occurred in the remaining 3 patients ($P>0\ 05$)

In one patient the fall in heart rate was transient (2 8 beats per min.) A more marked change occurred in one patient (No. 29) amounting to a maximum fall in heart rate of 17 6 beats per min.

Pulmonary artery pressures

Diastolic—The PAdp remained constant in 4 subjects but fell significantly in two (No. 36, $P<0.001$ and No 43 $P<0\ 01$) as shown in Fig.

The maximum individual change was from 15 4 to 12.8 mmHg and from 19.0 to 15.0 mmHg respectively In the former case there was an associated increase in cardiac output. In both subjects lowered PAdp were seen at the first measurements 15 minutes after the ouabain injection. There

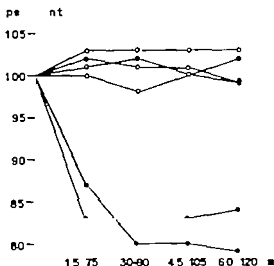


Fig 22. Pulmonary artery diastolic pressures expressed as per centage of the mean control value (=100) after 0.75 mg ouabain (n=6) The mean values are indicated for successive 1-hour periods after ouabain, each separated by 15 min Filled circles indicate s gnificant change at the 5 per cent level or less. Unfilled circles denote no significance.

TABLE 16 *Number of patients who showed significant haemodynamic changes after ouabain (n=6)*

	Heart rate	Pulmonary artery pressure			Aortic pressure			Pulse pressure	Stroke volume	Cardiac output	Systemic resistance	Left ventricular work	Left ventricular stroke work
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean						
Increase	1		0	1	5	3	5	6	4	2	0	4	4
No change	3	2	4	3	1	3	1	0	2	4	4	2	2
Decrease	2	2	2	2	0	0	0	0	0	0	2	0	0

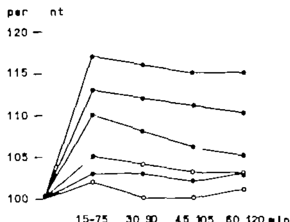


Fig 23 Aortic mean pressure expressed as per centage of the mean control value (=100) after 0 75 mg ouabain (n=6) The mean values are indicated for successive 1 hour periods after ouabain, each separated by 15 min Filled circles indicate significant change at the 5 per cent level or less. Unfilled circles denote no significance

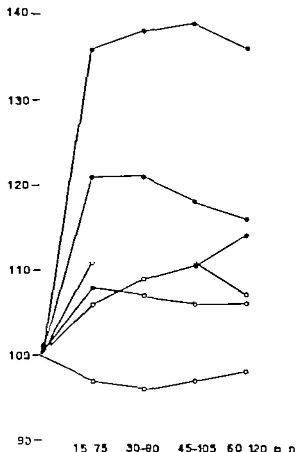
was a slight overall decrease in PAdp of 1 0 mmHg when the mean control values were compared with the mean values from the last 5 observations This decrease from 17 9 mmHg, S.D = ±3 6 to 16.9 mmHg, S.D = ±4.2 was not significant ($P>0.05$)

Mean—No significant change occurred in 3 patients ($P>0\ 05$) A significant, but transient, rise of 1.8 mmHg was seen in case 9 ($P<0.05$) whereas a significant fall was found in two (No. 36 $P<0\ 001$ and No 43 $P<0\ 01$) The mean control value for the 6 patients fell from 25 4 mmHg, S.D = ±3 2 to 24 3 mmHg, S.D = ±3 8 when compared to the mean value obtained from the last 5 observations ($P>0\ 05$)

Aortic pressures

Mean—The mean aortic pressure rose significantly in 5 of the 6 patients ($P<0.05$ Fig. 23) This change was usually most marked 15 to 30 minutes after ouabain In one patient (No 12) the rise was transient.

The mean control value, 98 6 mmHg, S D = ±18 7 did not differ significantly from the mean of the last 5 observations 104 3 mmHg, S D = ±18 3 ($P>0\ 05$) The *pulse pressure* rose rapidly and significantly in all 6 patients ($P<0.05$) In



F 4 S ke volume expressed as per centage of the mean ntro value (=100) after 0 75 mg ouabain (=6) The mean values are indicated for successive 1 hour periods after ouabain, each separated by 15 min. Filled rcles indicate significant change at the 5 per cent level r less Unfilled circles denote no significance.

two patients the change was transient. Again the maximum rise was observed early after the ouabain njection. The mean control value, 47.3 mmHg, S.D $= \pm 21$ 5 did not differ significantly from the mean of the last 5 measurements which was 53 5 mmHg, S.D $= \pm 23$ 1 for the 6 patients ($P > 0.05$)

St ke volum

Two patients (No 10 and No 1) showed considerable variation in their stroke volume during the control hour The results are shown in Fig. 24. There was a significant increase in 4 of the 6 patients (No 9 29 36 and 49 $P < 0$ 05) although it was transient in one (No. 49) The rise in stroke olume for all patients from the mean of the control alue (45 0 ml S.D $= \pm 24.2$) to the mean of the last 5 observations (48.4 ml, S D $= \pm 21$ 5) was 3 4 ml, which is not significant ($P > 0.05$)

Cardiac output

During the control period two patients showed marked variation in their cardiac output. These variations were not due to changes in heart rate. A significant rise ($P < 0$ 05) was observed in 2 of the 6 patients (No 9 and No 36) (Fig 25) In the remaining 4 patients no significant changes were observed ($P > 0.05$)

When comparing the mean control values with the mean of the last 5 observations there was an insignificant increase from 3.8 liters per minute, S.D $= \pm 1$ 5 to 4.0 liters per minute, S.D $= \pm 1$ 5 ($P > 0.05$)

Systemic esistance

There were no marked changes. A slight, yet significant decrease by a maximum of 229 dyn.sec. cm[5] ($P < 0.01$) was observed in one patient (No. 36) due to a proportionally marked increase in

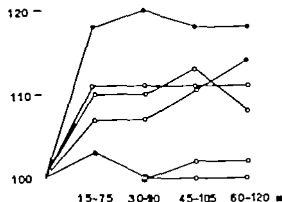
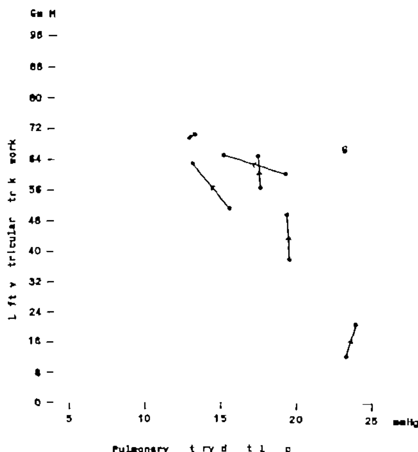


Fig 25 Cardiac output expressed as per centage of the mean control value (=100) after 0.75 mg ouabain (n=6) The mean values are indicated for successiv 1 hour periods after ouabain each separated by 15 min Filled circles indicate significant change at the 5 per cent level or less Unfilled circles denote no significance

Fig 26. Relationship between left ventricular stroke work and pulmonary artery diastolic pressures before and after 0 75 mg ouabain (n=6) Mean control values are compared with mean of values during second hour after ouabain.



cardiac output in association with a constant mean aortic pressure. A significant but transient decrease of 135 dyn.sec.cm [5] ($P<0.01$) was observed in a further patient (No 49) The mean control value of 2461 dyn sec.cm [5] S D $= \pm 982$ did not differ from the mean of the last 5 observations, 2410 dyn sec.cm [5] S.D $= \pm 1044$ for the 6 patients ($P>0.05$)

Left ventricular stroke work

This increased significantly in 4 patients (No 9 10 29 and 36) ($P<0.05$) the increase being of transient nature in one (No 10) The findings have been related to changes i PAdp in Fig 26 It should be noted that in one patient with the lowest stroke work values (No. 29) in this illustration there was a concomitant decrease in heart rate of 16.4 per cent. The mean control left ventricular stroke work for the 6 patients of 48 5 Gm.M., S D $= \pm 20$ 4 rose to a mean of 55 9 Gm. M., S.D $= \pm 18.5$ in the second hour after ouabain. This difference was however not significant ($P>0$ 05)

Left ventricular minute work

This increased significantly in the same 4 patients (No 9 10 29 and 36) ($P<0.05$) The mean control left ventricular minute work for the group of 4.1 kgm per min., S D $= \pm 1$ 4 did not differ from the mean of the last 5 observations which was 4.7 kgm. per min., S D $= \pm 1$ 5 ($P>0.05$)

Arrhythmias

One patient had significant decrease in rate of ventricular ectopic beats calculated per 15 minute periods ($P<0$ 05) and in a further patient there was a significant increase in supraventricular

ectopic beats during the first hour after ouabain administration ($P<0.05$) In no instance did AV block or ventricular fibrillation develop

Subjective reactions

In spite of the high ouabain dose no patients presented any symptoms suggesting digitalis over dosage. The only complaint registered concerned the lack of freedom of movement during the study

Complications

No complications attributable to the administration of 0 75 mg ouabain occurred.

DISCUSSION

Six patients with acute myocardial infarction and raised PAdp have been investigated haemodynamically before and after the administration of ouabain. This compound was chosen because of its rapid onset of action and elimination. The dosage in the present investigation was 0 75 mg ouabain for all cases. For routine digitalization purposes initial doses of 0.25 to 0 5 mg are commonly advised, (Wyckoff & Goldring 1927 Batterman et al. 1940, Chavez 1943 Gefter & Leaman 1943 and Goodman & Gilman 1965) In some investigations higher doses have been given to ensure adequate digitalization (Eichna & Taube 1944, Blomfield et al. 1948 Ahmed et al. 1950) At a dose of 1.0 mg Ahmed and co-workers (1950) recorded side-effects in the form of headache and systemic hypertension. The dosage of 0 75 mg ouabain in this study may therefore be regarded as a relatively high but safe dose which may be expected to have haemodynamic effects. Lown (1968) who considers a digitalis glycoside to be the agent of first choice for heart failure in acute myocardial infarction recommends that ouabain should be given in increments of 0 1 mg to a total dose of 0 4 to 0 8 mg in 24 hours.

The haemodynamic effects of rapid digitalization in patients with heart failure of varying severity but not due to acute myocardial infarction, have been investigated repeatedly with methods of increasing reliability over the last 40 years (Stewart & Cohn 1932, Stewart et al 1938. Berséus 1943, McMichel & Sharpey Schafer 1944, Bloomfield et al. 1948, Stead et al. 1948, Harvey et al. 1949 Lagerlöf & Werkö 1949 Ahmed et al. 1950 Bayliss et al. 1950 Werkö et al. 1958 Ferrer et al. 1960 Selzer & Malmborg 1962, Malmborg 1965 and Johansson 1966) An increase in cardiac output has been the usual finding The pulmonary artery pressure changes have been more variable and the selection of the patients investigated probably plays an important role (Harvey et al. 1949 Lagerlöf & Werkö 1949 Bayliss et al 1950 Varnauskas 1955 Werkö et al. 1958, Selzer & Malmborg 196., Malmborg 1965 Johansson 1966 and Johansson 1970)

Digitalis in myocardial infarction

In the present study a significant fall in PAdp within the first two hours after ouabain administration was observed in two of the 6 patients with acute myocardial infarction. The cardiac output increased in two subjects and 3 showed an increase in mean aortic pressures. Left ventricular work and stroke work increased significantly in 4 patients. Both patients who responded with a significant increase in cardiac output were amongst the 3 who had a history of previous angina pectoris and/or myocardial infarction.

Previous clinical studies.—Digitalis given on fairly wide indications in acute myocardial infarction was advocated by several clinical workers in the earlier part of this century (Herrick 1912, Hamman 1926, Edens 1934 and Blumberger 1938) These workers based their opinions on clinical impressions obtained from rather small patient groups without adequate control series Subsequently a more graded attitude developed. Apprehension appeared following reports of an increase in ventricular arrhythmias when digitalizing animals with experimental myocardial infarctions (Bellet et al. 1934, Travell et al. 1938 as well as more recently Hood et al. 1967 and Morris et al. 1967) Gold (1925) did not, on the other hand, find evidence of lowered digitalis tolerance in experimental infarcts. Cardiac rupture suspected to be a complication was also reported (Gans 1951) but this was not confirmed by Maher et al. (1956)

A valuable contribution allaying these, perhaps exaggerated, fears of the toxicity of digitalis in acute myocardial infarction in man was made by Askey (1951). He treated 50 patients with digitoxin and compared them with a control group. There were no more ventricular ectopic rhythms or instances of sudden death in the treated group.

In 1955 Boyer reported on 50 consecutive patients who were given digitalis with a resulting low mortality of 16 per cent. In 1959 Willems and Schüller reported on their careful investigation of 197 subjects with acute myocardial infarction, 125 of whom were digitalized for the same indications as in routine clinical cardiology. They found no signs of a lowered toxic threshold for cardiac glycosides in these patients and recommended digitalization in acute myocardial infarction along the same lines as in heart failure and certain arrhythmias of other aetiology. In their conclusions they confirmed previous opinions expressed by Schemm (1950), Ellis & Hancock (1957), Sanazaro (1957) and Busé (1958). A clinical report of interest is that of Gorlin & Robin (1955) who presented 4 cases with acute myocardial infarction in cardiogenic shock but who also had marked signs of pulmonary congestion. All responded with a rise in blood pressure and clinical improvement after receiving digitalis.

Some authors have considered that only fairly advanced bilateral heart failure is an indication for digitalization in acute myocardial infarction (Wollheim 1956). This restricted approach has been criticized by amongst others Aschenbrenner & Erdmann (1959) who point to the rarity of this clinical picture in acute myocardial infarction where pure left sided heart failure is the more common presentation. These authors also point to the improvement following digitalization in patients with acute myocardial infarction as judged by serial chest X-ray changes.

There is therefore evidence that digitalization in acute myocardial infarction does no harm to the patients. To obtain evidence of the usefulness of this therapy has been more difficult. Haemodynamic investigations in man on the effects of cardiac glycosides in myocardial infarction are scarce.

Digitalis in experimental infarction.—Pizza & Hammer (1961) found no marked haemodynamic changes following digitalization in dog experiments. Cronin & Zsotér (1965) studied the haemodynamic effects of acetylstrophanthidin in experimental cardiogenic shock in the dog following closed chest embolization. They found a significant rise in arterial blood pressure, cardiac output and left ventricular stroke work and a reduction in left ventricular end diastolic pressures in the shocked animals. They observed no marked changes in the peripheral resistance. Using ouabain Marano et al. (1966) arrived at similar results in experiments with shocked dogs although these workers did not find any significant improvement in left ventricular end diastolic pressure. Hood et al. (1969) also came to similar conclusions from open chest pig experiments finding that when acetyl strophanthidin had been given prior to coronary artery occlusion less marked haemodynamic changes were seen as regards aortic mean pressure, left ventricular dP/dt and also left ventricular end diastolic pressure.

Haemodynamic effects of digitalis in myocardial infarction in man.—Whereas considerable information is available from these animal experiments, less is known about the haemodynamic actions of digitalis in man following acute myocardial infarction. Malmcrona et al. (1966) followed the early haemodynamic effects following digitalis administration in 10 patients within 4 days of onset of symptoms. None were in heart failure but most had shown a substantial fall in blood pressure. These authors found a rise in systolic and mean brachial artery pressure not explained by either a rise in cardiac output or peripheral resistance.

Balcon et al. (1968) reported on the haemodynamic effects following rapid digitalization in 11 patients described as showing early signs of left ventricular failure. These authors had included pulmonary artery pressures in their evaluation. The mean pressure was within normal limits suggesting that the degree of heart failure in their patients was not marked. Their findings were a fall in cardiac output and cardiac work without any significant changes in systemic blood pressure or peripheral

resistance following digitalis administration. No change in mean pulmonary artery pressure was observed.

In addition a preliminary report has recently been presented by Hodges et al. (1969) on the effects of digoxin in subjects with left ventricular failure in acute myocardial infarction. Their study is more comparable with the present one in that a raised PAdp (mean 14 mmHg) was present. On the other hand the mean cardiac index was normal. These authors concluded that only two of the 6 patients showed improved left ventricular function as suggested by a positive inotropic shift when plotting stroke work index against PAdp after digitalis. *Only one of their patients had a fall in PAdp*

The material has varied considerably in the three investigations of patients available, and conclusions are therefore not as easily obtained. The haemodynamic changes observed in the present study are in good agreement with those of Malmcrona et al. (1966) as regards the increase in systemic pressure, although their group was not in clinical failure. In contrast it was not possible to confirm Balcon and co-workers finding (1968) of a reduced cardiac output and no changes in arterial pressures following digitalization, the latter effect possibly being dose dependant.

The present author noted that in two patients in whom the PAdp did not change after ouabain there was a rise in left ventricular stroke work. Further, in two patients in whom the PAdp fell the left ventricular stroke work rose. If as is suggested in the earlier part of this study PAdp levels reflect left ventricular filling pressures, then these changes may indicate improved left ventricular performance after ouabain. They are comparable to the changes described to occur in two of the 6 patients in the study of Hodges et al. (1969) The apparent improvement in left ventricular performance in patient No. 29 with very low left ventricular stroke work values, shown in Fig. 26 may be explained by a marked reduction in heart rate alone (Berglund et al. 1958)

Account must be taken of the fact that the present group, even when compared to the patients of Hodges and co-workers showed a more severely affected haemodynamic state. The mean PAdp in the present series was 17.9 mmHg, S.D $= \pm 3.6$ and associated with a mean cardiac index of 2.1 liters per min. per m^2 S.D $= \pm 0.8$. The equivalent findings in the patient group of Hodges et al. was 14 mmHg, S.D $= \pm 2.0$ *and* 3.3 *liters per min. per* m^2 S.D $= \pm 0.5$

SUMMARY

The purpose of this part of the present investigation was to determine what, if any effects the cardiac glycoside ouabain had on the haemodynamic state of patients with raised PAdp suggesting left heart failure in acute myocardial infarction. Particular interest was placed on changes in the PAdp, cardiac output and left ventricular stroke work. All patients were in sinus rhythm.

Ouabain 0.75 mg, administered to 6 patients according to these criteria was found to lower the PAdp significantly in two and increase the cardiac output also in two during an observation period of two hours In one patient both of these changes were observed. The left ventricular stroke work rose in 4 patients. Aortic pressure increased in 5 and pulse pressure in all 6 patients The change in relationship between left ventricular stroke work and PAdp in 4 of the 6 patients may indicate an improvement in left ventricular function.

Patients

Eight patients were investigated There were 7 men and one woman. Their mean age was 60 years, with a range from 45 to 71 years. The diagnosis was made in all on a typical history of central chest pain, and confirmed by a characteristic enzyme rise and electrocardiographic pattern Furthermore autopsy confirmed the diagnosis in the patients who died. Four of the patients had predominantly anterior infarcts and in the other 4 it was posterior Table 15 gives the salient clinical and laboratory features of this group

Three in the present group of 8 patients had taken part in the ouabain trial and had therefore received 0 75 mg ouabain 6 hours before commencement of this study

In addition to raised PAdp all patients had basal rales, although in one patient these were only few and scattered A third heart sound was present in 5 patients and these patients also showed chest X-ray changes consistent with pulmonary congestion amounting to pulmonary oedema in two In two subjects the chest X-rays had been taken when the PAdp were considerably lower than at the time of the frusemide trial Five patients were examined on the first day of the illness, the remaining three on the second day the trial always being carried out on the first day of hospitalization.

Results

The mean values for the patient group obtained during the control period were as follows PAdp 17 3 mmHg, S.D = ±3 1 The mean cardiac output was 4 3 liters per min S D = ±0 9 and stroke volume mean 30 7 ml. S.D = ±16.6 The mean heart rate was 87 9 beats per min., S.D = ±13 0 The patients were asked to micturate immediately prior to the frusemide injection and also at the end of the investigation. Catheterization of the bladder for purposes of exact evaluation of the diuresis was not carried out. Following the frusemide injection (40 mg) there was a mean diuresis during the two hours of 1408 ml, range 950 to 2650 ml.

The haemodynamic data are presented in Table B of the Appendix. In Table 17 a summary of the patients showing significant haemodynamic changes is presented.

Heart rate

If the mean of the control values for the whole group is compared with the mean obtained from the last 5 estimations, there was an insignificant fall of 0 1 beats per min. from 87 9 beats per min., S.D = ±13.0 to 87 8 beats per min S.D = ±12.4 ($P > 0.05$) A significant rise in heart rate was seen in 3 subjects (No 10 40 and 49 $P < 0.05$) In 2 of these the rise was transient. In 3 patients no change occurred and in 2 (No 7 and 9) a significant decrease was found ($P < 0.01$)

Pulmonary artery pressures

Diastolic A significant decrease was found in all patients after frusemide ($P < 0.05$) (Fig 27) The fall in PAdp was usually seen 15 or 30 minutes after the diuretic had been given. In 5 patients values within the normal range, i.e. 11 mmHg or lower were obtained at the last 2 determinations. When comparing the mean control values for the whole group with the mean values obtained during the last 5 estimations there was a significant decrease by 5 3 mmHg from 17 3 mmHg, S.D = ±3 1 to 12.0 mmHg, S.D = ±4.3 ($P < 0.05$) The findings are also illustrated in Fig. 30

No significant relationship was obtained when the fall in PAdp expressed in either per cent of the control value or in mmHg was compared with the diuresis ($r = 0.48$ and 0.41 respectively $P > 0.05$)

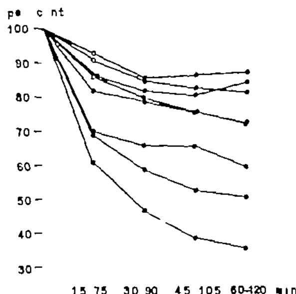


Fig 27 Pulmonary artery diastolic pressures expressed as percentage of mean control values (=100) after 40 mg frusemide (n=8) The mean values are indicated for successive 1-hour periods after frusemide, each separated by 15 min. Filled circles indicate significant change at the 5 per cent level or less. Unfilled circles denote no significance

Systolic—This remained unchanged in one patient (No 12) after the frusemide injection and fell significantly in the other 7 ($P<0.05$) When comparing the mean control values for the whole group with the mean values obtained during the last 5 estimations there was a significant decrease for the group by 9.2 mmHg from 38.6 mmHg, S.D = ±4.4 to 29.4 mmHg, S.D = ±4.5 ($P<0.01$)

Mean—A significant decrease following frusemide injection was also found as regards pulmonary artery mean pressures in all patients ($P<0.05$) The mean control values for the 8 patients decreased significantly by 6.9 mmHg from 25.6 mmHg, S.D = ±2.9 to 18.7 mmHg, S.D = ±4.6 for the last 5 observations ($P<0.01$)

Aortic p essures

Mean—When the mean control values for the entire group were compared w th the mean value obtained from the last 5 estimations, there was a minor and insignificant overall decrease by 3.8 mmHg from 111.8 mmHg, S.D = ±16.3 to 108.0 mmHg,

TABLE 17 *N mber of patients who showed significant haemodynamic changes after frusemide (n=8)*

	Heart rate	Pulmonary artery pressure			Aortic pressure			Pulse pressure	Stroke volume	Cardiac output	Systemic resistance	Left ventricular work	Left ventricular stroke work
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean						
Increase	3	0	0	0	1	1	0	0	0	0	2	0	0
No change	3	1	0	0	4	5	5	4	4	4	6	5	6
Decrease	2	7	8	8	3	2	3	4	4	4	0	3	2

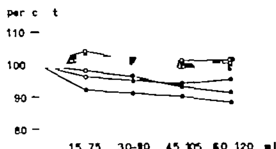


Fig 28. Aortic mean pressure expressed as percentage of mean control alues (=100) after 40 mg frusemide (=8) The mean alues are indicated for successiv 1 hour periods after frusemide, each separated by 15 min. Filled circles indicate significant change at the 5 per cent level or less Unfilled circles denote no significance

S.D = ±15 7 ($P>0.05$) The mean aortic blood pressure fell significantly in 3 patients (No. 7 9 and 49 $P<0.01$) (Fig. 28)

The pulse pressures fell significantly in 4 pa tients (No 7 9 12 and 49 $P<0.05$) No signifi cant difference was obtained when the mean con- trol values for the entire group were compared with those obtained from the last 5 estimations, there being a sl ght decrease by 2 7 mmHg from 62 9 mmHg, S.D = ±21 9 to 60.2 mmHg, S.D = ±20 0 ($P>0.05$)

Stroke volume

Four patients (No 9 12 43 and 49) showed a significant reduction n stroke volume after fruse mide ($P<0 05$) the decrease being transient in one (No 12) No significant changes were ap- parent when the mean control values for the whole group 50 8 ml. S.D = ±16 6 were compared with the mean values obtained from the last 5 estimations, there being a decrease by 3 0 ml to 47.8 ml. S D = ±15.8 ($P>0 05$)

Cardiac outp t

The same 4 patients who showed a reduced stroke olume also had s gnificant decrease n cardiac output ($P<0 05$) (F g 29) This decrease was due to reduced stroke olumes. On the other hand no s gnificant change was apparent when the mean control values for the entire group were com- pared with those from the last 5 estimations, there being a decrease by 0 2 liters per min., from 4 3 liters per min., S.D = ±0 9 to 4.1 liters per min., S.D = ±0 9 ($P>0.05$)

No significant relationship was found when plotting the decrease in cardiac output against decrease in PAdp (r=0 19) Nor was a significant relationship between fall in cardiac output and diuresis obtained

Left ventricular strok wo k

Two patients (No. 9 and 49) showed a signifi- cant reduction in stroke work ($P<0.05$) Again no significant change was found in the group as a whole when comparing the mean control values of 63 6 Gm.M., S.D = ±14 9 with the mean of the final 5 estimations, 60.8 Gm.M., S.D = ±16._ These findings have been related to the fall i PAdp and are illustrated in F g. 30

Left ve tricular minute work

Three patients (No 9 12 and 49) decreased their minute work significantly ($P<0 05$) In No. 12 this fall was transient. Agai no significant changes were found for the group as whole, the mean level for the control period of 5 4 kgm per min., S.D = ±0.8 not differing from 5.3 kgm per min., S.D = ±1 1 obtained from the last 5 estima tions ($P>0.05$)

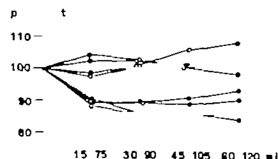


Fig 29 Cardiac output expressed as percentage of mean control alues (=100) after 40 mg frusemide (n=8) The mean alues are indicated for successiv 1-hour pe riods after frusemide, each separated by 15 min. Filled circles indicate significant change at the 5 per cent level or less. Unfilled circles denote no significance.

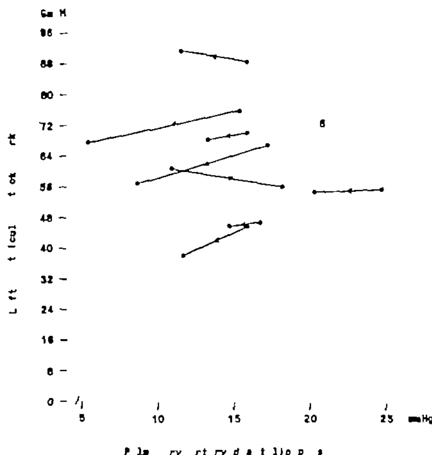


Fig 30 Relationship between left ventricular stroke work and pulmonary artery diastolic pressures before and after 40 mg frusemide (=8) Mean control values are compared with the mean of values during second hour after frusemide.

Systemic resistance

A slight, but significant increase in calculated systemic resistance due to reduced cardiac output values associated with constant mean aortic pressures was seen in 2 patients (No. 12 and 43 $P<0.05$) being transient in one (No 12) The maximum increase was 167 and 380 dyn.sec.cm⁻⁵ respectively No significant differences were found when the mean control values for the entire group were compared with the mean values from the last 5 observations, there being a slight overall increase by 41 dyn.sec.cm⁻⁵ from 2154 dyn.sec.cm⁻⁵ S.D $= \pm 570$ to 2195 dyn.sec.cm⁻⁵ S.D $= \pm 568$ ($P>0.05$)

Subjective reactions

A few patients found the lack of freedom of movement during the study tiresome.

Complications

No significant increase in the frequency of ventricular ectopic beats or other arrhythmias was recorded in any case when the incidence per 15 minute periods before and after frusemide was compared.

DISCUSSION

In 8 patients with left heart failure as defined by a raised PAdp due to acute myocardial infarction 40 mg frusemide has shown consistent haemodynamic changes for two hours after the drug was given. In all 8 cases the pulmonary artery diastolic pressures dropped significantly This was found both at intraindividual and group comparison. The fall in pressure was usually rapid and commonly seen within 30 minutes after the frusemide injection. There was a diuresis in all, mean 1408 ml with a range of 950 ml to 2650 ml. The PAdp fell to normal values in 5 of 8 patients.

A significant reduction in systemic arterial mean pressure, pulse pressure, cardiac output, and stroke volume and left ventricular stroke work was seen in some patients, although not when the mean con-

trol values for the group were compared with mean values for the second hour after frusemide administration. The changes observed in left ventricular stroke work and PAdp after frusemide were compatible with a movement along a depressed left ventricular function curve.

The reason for choosing frusemide in this trial was its rapid action. In the early stages of acute myocardial infarction demands of rapid onset rather than prolonged action is the common requirement of a diuretic. The dosage of 40 mg was based on a scrutiny of 20 patient hospital records to see which dose of frusemide intravenously gave a diuresis of approximately one liter in subjects with acute myocardial infarction. It was felt unwise to use larger doses for fear of provoking too rapid a reduction of blood volume in these patients with heart failure, in whom an increased blood volume is not a prominent feature. Additionally a fall in blood pressure was thought to be a possible consequence. These considerations are important since the dose chosen should be constant in all cases studied.

The literature on the haemodynamic changes following the administration of diuretics is sparce (Stampfer et al. 1968) and does not include reports on patients with acute myocardial infarction.

A rise in cardiac output associated with a fall in right atrial pressure has been found following a single intravenous injection of a mercurial diuretic in subjects with heart failure not due to acute myocardial infarction by Pugh & Wyndham (1949). In contrast a reduced cardiac output was reported by Dustan et al. (1959) in non-acute experiments with chlorathiazide in hypertensive subjects. Rowe et al. (1962) confirmed a fall in cardiac output as well as finding lowered mean pulmonary artery pressures in their haemodynamic investigation of the acute effects of intravenous chlorothiazide in patients with hypertension. Subsequently these findings of a fall in pulmonary artery mean pressures have been confirmed in non-acute experiments by Rader et al. (1964) who employed mercurial diuretics in patients with congestive heart failure, and by Stampfer et al. (1968) who used thiazides in patients with rheumatic valvular disease. The latter authors also demonstrated a reduction in cardiac output.

Recently Lal et al. (1969) investigated the acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressures, the latter being patients with mitral valvular disease. In the patients with normal mean atrial pressures the major haemodynamic change was a fall in cardiac output due to a reduction in stroke volume associated with an increase in systemic vascular resistance. Similar findings were obtained in the patients with increased left atrial pressures in whom a reduction in mean pulmonary artery pressures was also seen.

The present investigation in patients with acute myocardial infarction also shows a significant reduction in elevated pulmonary artery pressures, whereas the decrease in stroke volume, cardiac output and left ventricular stroke work is of lesser magnitude. This was also the case for the increase in calculated systemic resistance.

Little is known of the effects on the pulmonary circulation which follow frusemide. The likliest explanation is that the reduction in total blood volume following the diuresis will exert its primary beneficial effect on the most overloaded circulatory compartment. In the case of pure left sided heart failure this will be the pulmonary circulation.

Some clinical observations have questioned such a simple mechanism. Biagi & Bapat (1967) described a patient with pulmonary oedema who improved rapidly on receiving frusemide intravenously without any accompanying diuresis. They suggested that frusemide first caused fluid to be removed from the pulmonary circulation and that this was later followed by a diuresis. This hypothesis recieved support in the investigation of Bhatia et al. (1969). They examined the effects of intravenous frusemide in 7 patients recovering from high altitude pulmonary oedema. The pulmonary blood volume decreased within 15 minutes, and before the onset of diuresis. Their other findings included a fall in cardiac output but no change in pulmonary artery pressures, which were near or within the normal range.

In the present study the haemodynamic changes after frusemide occurred rapidly The author was reluctant to introduce a urinary catheter in these patients and so the exact timing of the onset of the diuresis is not available.

It has been suggetsed that the use of diuretics in acute myocardial infarction may be associated with the precipitation of ventricular fibrillation (McDonald 1968) None of the patients in the present study showed a s gnificant increase in the frequency of ventricular ectopic beats.

SUMMARY

The haemodynamic changes which follow an injection of frusemide 40 mg have been followed in 8 patients with acute myocardial infarction in sinus rhythm and with raised PAdp suggesting left heart failure.

A constant finding was a fall in pulmonary artery diastolic and mean pressures. Furthermore a variable but slight reduction in mean aortic pressure, cardiac output, stroke volume and left ventricular work and stroke work was observed.

A COMPARISON OF THE HAEMODYNAMIC EFFECTS OF OUABAIN AND FRUSEMIDE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND A RAISED PULMONARY ARTERY DIASTOLIC PRESSURE

An attempt was made to study both frusemide and ouabain in the same patients whenever possible. However a prerequisite of the design of the trial was that a raised PAdp should still be present for a second drug to be given. As frusemide usually lowered PAdp, and owing to the rapid deterioration of one patient (No 29) in the ouabain study only 5 of the 9 patients were in fact investigated before and after both drugs (No. 9 10 12, 36 and 49)

The one common haemodynamic change expected after both ouabain and frusemide was a decrease in the pulmonary artery pressure. Frusemide lowered the PAdp significantly in 8 out of 8 patients, whereas ouabain lowered it in only 2 of the 6 investigated. This difference is statistically significant ($P<0.05$) The corresponding findings expressed in per cent of the control values are given in Table 18

Other differences in the haemodynamic effects of the two drugs are not of equal interest as the mechanism of action of the two drugs differs

The changes observed in aortic pulse and mean pressures, cardiac output, stroke volume and left ventricular work and stroke work were in opposite directions after the two drugs It is possible that these opposing effects may be modified if both drugs were given simultaneously

When considering the haemodynamic alterations observed in per cent after ouabain and frusemide respectively Table 18 it will be seen that the most marked change was that observed in the pulmonary artery diastolic pressure after frusemide. Associated with this was a minor decrease in aortic mean pressure, cardiac output, stroke volume and left ventricular stroke work. In contrast, ouabain resulted in only a minor fall in the PAdp but was associated with a small increase in cardiac output, stroke volume, mean aortic pressure and left ventricular work and stroke work.

In the type of patient investigated, i e. with moderate to severe left heart failure associated with an acute myocardial infarction it is probable that a fall in PAdp indicates a beneficial effect. Whether the small increase in cardiac output, stroke volume, aortic pressure and left ventricular stroke work which was seen in this investigation after ouabain is of benefit is open to question. After ouabain the changes in left ventricular stroke work and PAdp in 4 of the 6 patients suggest a modest improvement in left ventricular performance. Clearly a marked rise in cardiac output and aortic pressure in patients with acute myocardial infarction would be undesirable because of the associated increase in left ventricular work and myocardial oxygen consumption. Similarly a marked fall in cardiac output and mean aortic pressure would be undesirable as

TABLE 18 Changes in haemodynamic variables following ouabain and frusemide administration in patients with acute myocardial infarction and raised PA_{dp}. The figures represent change in per cent when comparing the mean value from the second hour after the drug was given with those of the control hour

	0 75 mg (n=6) Ouabain	40 mg (n=8) Frusemide
Pulmonary artery pressure		
Diastolic	— 6	—31
Mean	— 3	—27*
Aortic pressures, mean	+ 6	— 4
Cardiac output	+ [illegible]	— 6
Stroke volume	+ [illegible]	— 6
Left ventricular work	+15	— 2
Left ventricular stroke work	+15	— 4

(*) denotes significance for entire group.

the perfusion of the coronary cerebral and renal vascular beds would be prejudiced.

The present investigation therefore has shown that frusemide is followed by a reduction in PAdp and this probably indicates a fall in left ventricular filling pressures. It is likely that this change was beneficial After ouabain the changes in left ventricular stroke work and PAdp in 4 of the 6 patients may suggest a modest improvement in left ventricular performance. More rigid conclusions are not warranted from this limited study Further information is needed and will probably best be obtained from larger scale clinical studies of cardiac glycosides and diuretics performed in patients with moderate heart failure after acute myocardial infarction

GENERAL SUMMARY

The aim of the present investigation was to study certain aspects of the left heart failure seen in the early stages of an acute myocardial infarction. The study consists of three parts, one clinical, one haemodynamic and the third therapeutic.

PART I In Part I an evaluation of the findings as regards left heart failure from 363 consecutive admissions to a coronary care unit (CCU) is presented. Only the findings observed during the first 24 hours were taken into account.

1 An increase in mortality associated with left heart failure was confirmed. This remains in spite of CCU-care. 43 per cent of the patients had signs of failure on admission, and there was a significant rise during the first 24 hours to 66 per cent which was not associated with a concomitant increase in mortality

2 Patients with left heart failure had a higher incidence of larger infarctions. There were more patients with anterior as opposed t posterior infarcts. There was a greater incidence of severe arterial hypoxaemia in the patients with failure.

3 Patients with a history of previous heart failure were significantly older and this group included significantly more women than the group who were previously fully compensated

4.Of those patients who had heart failure on admission and during the first 24 hours in the CCU the mortality in the CCU was significantly higher in those who did not have a past history of heart failure.

In contrast, patients with a past history of heart failure had a significantly higher after-care mortality if they had heart failure on admission or during the first 24 hours in the CCU

5 The severity of clinical left heart failure was of greater prognostic value in the patients without a past history of heart failure as compared to those with previous heart failure.

6. The association between large infarct size and arterial hypoxaemia in the patients with heart failure was valid in the whole group and in those who did not ha e a past history of heart failure.

PART II In Part II a haemodynamic study of 50 patients with acute myocardial infarction is presented The patients had not received treatment for heart failure prior to catheterization. The pulmonary artery diastolic pressure, which reflects left heart filling pressures, was taken as the reference parameter The study i volved flow guided catheterization of the pulmonary artery at the bedside on the first morning in the CCU These patients with acute myocardial infarction were all in sinus rhythm and had been selected to exclude patients who had other cardiovascular causes for abnormal haemodynamic findings A comparison was made between the PAdp and clinical and laboratory changes observed in patients with heart failure and myocardial nfarction. In addition in 18 of the patients the cardiac output and stroke volume were measured.

1 A moderate correlation was found between the PAdp levels and the infarct size as estimated by the maximum GOT elevation.

2 An levated PAdp was generally associated with arterial hypoxaemia.

3 Elevated PAdp values were associated with a poor prognosis.

4 Elevated PAdp values were associated with an increased number f pulmonary rales at auscultation, dyspnoea, increased heart rates, a third heart sound and pulmonary congestion on the chest X ray An analysis of error ratios suggested that the presence of rales on auscultation was the best indicator of an elevated PAdp The chest X ray was the next best guide to an elevated PAdp, although a number of patients with a raised PAdp had a normal chest X-ray

5 An elevated PAdp correlated well with a low cardiac output and stroke volume

PART III In this part the early haemodynamic effects of a cardiac glycoside, ouabain, and a potent diuretic, frusemide (Lasix®) are reported in 9 patients with acute myocardial infarction who had elevated PAdp levels. For the purpose of comparison a cross over trial with both drugs was performed as often as possible. To be included in this part of the study the patients PAdp had to be greater than 15 mmHg. Ouabain 0 75 mg and frusemide 40 mg were both given as a single injection through the pulmonary artery catheter Haemodynamic measurements were made for a control period of one hour before each drug was given and for two hours thereafter

1 The PAdp levels fell significantly in all 8 patients who received frusemide and this change was accompanied by a diuresis In 5 patients the PAdp had fallen to normal levels by the end of two hours.

2 The PAdp level fell significantly in only 2 of 6 patients who received ouabain.

3 Frusemide therefore resulted in a more constant fall in PAdp than did ouabain. This difference was significant.

4 The fall in PAdp after frusemide was associated with a small but insignificant overall reduction in cardiac output, stroke volume, aortic mean pressure, and left ventricular stroke work.

5 The administration of ouabain resulted in a small but insignificant overall increase in cardiac output, stroke volume, aortic mean pressure and left ventricular stroke work.

6 The reduction in PAdp seen after frusemide probably reflects a fall in left ventricular filling pressures. It is likely to be a beneficial effect as this decrease was not associated with a marked fall in cardiac output or aortic pressures

7 The haemodynamic changes after ouabain were in general less dramatic. However in 4 of the 6 patients the changes in left ventricular stroke work and PAdp may be consistent with a modest improvement in left ventricular performance

APPENDIX

TABLE A Haemodynamic findings in 6 patients before and after 0 75 mg ouabain

Case 9

	Control period					After ouabain							
Time (min)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min)	88	88	89	87	86	90	87	86	87	87	84	87	85
Pulmonary artery pressure (mmHg) systolic	43	42	43	45	45	47	48	47	45	46	40	43	44
diastolic	18	19	20	21	19	18	20	20	19	21	19	18	19
mean	27	28	28	29	29	31	31	31	28	29	27	27	28
Aortic pressure (mmHg) systolic	140	140	143	140	140	—	170	163	160	163	153	157	157
diastolic	83	83	83	80	80	—	97	93	93	93	87	87	87
mean	107	107	110	107	107	—	124	124	120	1 0	117	117	117
Pulse pressure (mmHg)	57	57	60	60	60	—	73	70	67	70	66	70	70
Cardiac output (l/min)	2 9	2 8	2 8	2.8	—	2 8	2 9	2.7	3 4	3 1	3 0	3 1	3.0
Stroke volume (ml)	33	32	31	32	—	31	33	31	39	36	36	36	35
Left ventricular work (kgm/min)	3 5	3 4	3 4	3 3	—	—	4.1	3 8	4.7	4.2	4 0	4 2	4 0
Left ventricular stroke work (Gm M.)	40	38	38	37	—	—	47	44	54	53	48	48	47
Systemic resistance (dyn sec.cm⁻⁵)	2949	3054	3140	3054	—	—	3417	3670	2821	3093	3117	3016	3117

Case 10

	Control period					After ouabain							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min)	79	81	72	85	82	82	75	84	82	82	83	82	82
Pulmonary artery pressure (mmHg) systolic	35	37	36	44	40	41	38	43	40	38	39	42	42
diastolic	16	18	16	20	17	19	17	19	17	17	18	17	17
mean	27	27	27	32	28	28	26	29	26	26	26	28	28
Aortic pressure (mmHg) systolic	130	123	113	123	130	137	147	140	143	133	133	127	127
diastolic	87	90	80	87	93	97	100	97	100	93	90	90	87
mean	103	103	100	107	110	1 0	120	117	113	107	110	107	110
Pulse pressure (mmHg)	43	33	33	36	37	40	47	43	43	40	43	37	40
Cardiac output (l/min.)	3 5	4 6	—	3 9	—	4.2	4.2	4 8	4 1	4 8	4 2	4.5	3.8
Stroke volume (ml)	44	57	—	46	—	51	56	57	50	59	51	55	46
Left ventricular work (kgm/min)	4 1	5 3	—	4 6	—	5 8	5 9	6 4	5 4	5 9	5 3	5 5	4 8
Left ventricular stroke work (Gm M.)	52	66	—	54	—	70	78	76	65	72	64	67	58
Systemic resistance (dyn sec.cm⁻⁵)	2332	1790	—	2193	—	2283	2285	1948	2203	1782	2093	1900	313

Case 12

		Control period					After ouabain							
Time (min.)		00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)		71	71	72	73	74	73	73	73	76	77	73	77	73
Pulmonary artery pressure (mmHg)	systolic	34	34	32	34	32	38	34	34	34	35	—	30	32
	diastolic	12	13	13	13	13	14	13	12	12	13	—	14	13
	mean	20	21	20	20	20	23	21	20	21	21	—	0	21
Aortic pressure (mmHg)	systolic	100	100	100	102	96	112	104	102	100	98	100	102	107
	diastolic	57	55	55	58	57	62	58	57	53	53	56	55	60
	mean	74	70	70	74	71	80	77	75	73	73	74	75	75
Pulse pressure (mmHg)		43	45	45	44	39	50	48	45	47	45	44	47	47
Cardiac output (l/min.)		—	6.1	7.0	6.0	—	6.6	6.0	6.4	6.6	6.4	6.5	6.5	6.6
Stroke volume (ml)		—	86	97	82	—	90	82	85	87	83	89	84	88
Left ventricular work (kgm/min.)		—	4.7	5.4	5.0	—	5.9	5.2	5.3	5.5	5.2	—	5.4	5.6
Left ventricular stroke work (Gm M.)		—	67	75	68	—	81	71	73	72	68	—	70	74
Systemic resistance (dyn.sec cm⁻⁵)		—	917	799	916	—	969	1026	937	884	912	919	922	908

Case 29

		Control period					After ouabain							
Time (min.)		00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)		117	106	104	105	104	93	93	91	87	89	90	91	91
Pulmonary artery pressure (mmHg)	systolic	33	31	31	35	37	36	38	39	38	38	40	37	37
	diastolic	22	22	22	23	23	24	4	24	24	24	4	24	23
	mean	26	25	25	28	29	27	29	28	28	28	29	28	27
Aortic pressure (mmHg)	systolic	103	101	98	99	104	130	132	115	116	120	115	118	115
	diastolic	71	71	70	71	76	86	84	79	79	83	79	80	79
	mean	83	80	82	82	84	98	101	94	93	96	93	95	94
Pulse pressure (mmHg)		32	30	28	28	28	44	48	36	37	37	36	38	36
Cardiac output (l/min.)		1.8	1.9	—	1.6	—	2.0	2.0	2.0	2.0	1.8	2.1	2.1	1.8
Stroke volume (ml)		15	18	—	15	—	22	22	22	23	20	3	23	20
Left ventricular work (kgm/min.)		1.5	1.5	—	1.2	—	2.0	2.1	1.9	1.9	1.8	2.0	2.0	1.7
Left ventricular stroke work (Gm M.)		12	14	—	12	—	22	23	21	22	20	2	22	19
Systemic resistance (dyn sec cm⁻⁵)		3685	3365	—	4096	—	3916	4035	3756	3716	4262	3539	3615	4174

Case 36

	Control period					After ouabain							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	92	91	91	91	93	86	86	89	90	96	95	94	98
Pulmonary artery pressure (mmHg) systolic	37	36	34	35	34	36	31	30	31	34	8	27	27
diastolic	16	16	15	15	15	13	13	12	12	11	13	13	15
mean	24	23	23	23	23	21	19	19	20	21	19	18	18
Aortic pressure (mmHg) systolic	116	119	122	119	122	128	130	125	126	127	127	123	127
diastolic	85	92	87	89	90	90	89	88	89	90	91	90	93
mean	99	103	102	102	104	107	107	104	105	103	105	105	107
Pulse pressure (mmHg)	31	27	35	30	32	38	41	37	37	37	35	33	34
Cardiac output (l/min.)	—	4.1	—	3.8	4.0	5.0	4.6	4.8	5.0	5.0	4.6	4.3	4.8
Stroke volume (ml)	—	45	—	42	43	57	53	54	56	52	48	46	49
Left ventricular work (kgm/min.)	—	4.9	—	4.5	4.8	5.2	5.9	6.0	6.3	6.1	5.8	5.4	6.1
Left ventricular stroke work (Gm M.)	—	53	—	50	52	60	68	68	71	63	60	58	63
Systemic resistance (dyn sec cm^{-5})	—	2008	—	2145	2078	2138	1859	173	1678	1646	1824	1952	1782

Case 49

	Control period					After ouabain							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	84	84	83	79	85	82	80	79	79	82	81	82	82
Pulmonary artery pressure (mmHg) systolic	37	39	40	42	39	42	37	35	37	38	35	39	36
diastolic	19	19	19	20	18	0	17	16	16	11	13	17	15
mean	25	25	29	26	6	27	25	21	23	22	22	25	23
Aortic pressure (mmHg) systolic	178	171	177	173	172	190	180	178	174	175	179	184	182
diastolic	95	85	90	85	89	93	91	85	82	84	84	88	88
mean	133	121	125	119	120	137	125	124	119	125	124	131	129
Pulse pressure (mmHg)	83	86	87	88	83	97	89	93	92	91	95	96	94
Cardiac output (l/min.)	3.6	3.3	3.5	—	—	3.6	3.6	3.6	3.4	3.6	3.5	3.5	3.7
Stroke volume (ml)	43	39	42	—	—	44	45	46	43	44	43	43	45
Left ventricular work (kgm/min.)	5.6	4.6	5.0	—	—	5.7	5.3	5.3	4.8	5.3	5.3	5.4	5.7
Left ventricular stroke work (Gm M.)	67	54	61	—	—	70	66	68	60	65	65	67	70
Systemic resistance (dyn sec cm^{-5})	2953	2930	2854	—	—	3041	2775	2753	2797	2731	2831	2991	2786

TABLE B Haemodynamic f ndi gs i 8 patient befor and after 40 mg fru mide

Case 7

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	104	103	105	105	102	101	106	102	96	100	99	93	92
Pulmonary artery pressure (mmHg) systolic	32	38	40	37	38	31	26	36	35	28	30	26	27
Pulmonary artery pressure (mmHg) diastolic	17	19	18	18	18	11	10	15	13	11	11	9	10
Pulmonary artery pressure (mmHg) mean	23	26	27	25	25	21	17	21	25	19	19	17	18
Aortic pressure (mmHg) systolic	163	163	169	164	165	162	157	157	162	157	159	117	159
Aortic pressure (mmHg) diastolic	77	79	80	78	76	78	70	73	78	77	76	69	75
Aortic pressure (mmHg) mean	113	113	115	113	111	115	101	107	110	107	108	101	108
Pulse pressure (mmHg)	86	84	89	86	89	84	87	84	84	80	83	78	84
Cardiac output (l/min.)	4.3	4.4	4.3	4.9	—	4.6	5.0	4.5	4.7	4.5	4.4	4.1	4.4
Stroke volume (ml)	41	43	41	48	—	44	47	44	49	45	44	47	48
Left ventricular work (kgm/mi)	5.6	5.6	5.7	6.3	—	6.3	6.4	5.6	6.2	5.9	5.8	5.5	5.9
Left ventricular stroke work (Gm M.)	54	55	51	62	—	60	60	55	65	59	58	59	64
Systemic resistance (dyn sec cm)	2100	2052	2137	1844	—	1998	1662	1900	1870	1900	1962	1835	1962

Case 9

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	93	93	89	90	88	91	86	85	84	83	85	82	86
Pulmonary artery pressure (mmHg) systolic	38	37	35	37	38	39	32	31	31	28	30	33	29
Pulmonary artery pressure (mmHg) diastolic	16	16	14	16	17	17	14	13	12	12	12	11	11
Pulmonary artery pressure (mmHg) mean	23	21	22	21	24	21	20	18	18	17	19	19	17
Aortic pressure (mmHg) systolic	140	147	140	140	140	140	133	133	127	121	133	130	127
Aortic pressure (mmHg) diastolic	80	83	80	80	80	80	73	73	70	67	73	73	70
Aortic pressure (mmHg) mean	107	110	107	107	107	107	100	100	97	93	100	93	93
Pulse pressure (mmHg)	60	64	60	60	60	60	60	60	57	57	60	57	57
Cardiac output (l/min.)	—	3.5	3.2	3.1	3.5	3.4	2.6	2.8	2.7	2.9	2.8	2.9	2.9
Stroke volume (ml)	—	38	36	34	38	37	30	33	32	35	33	35	34
Left ventricular work (kgm/min.)	—	4.5	4.3	3.8	4.0	4.2	3.0	3.3	3.1	3.2	3.4	3.2	3.2
Left ventricular stroke work (Gm M.)	—	49	46	42	47	45	35	39	37	39	39	39	38
Systemic resistance (dyn sec cm)	—	2312	2672	2759	2591	2515	3074	2854	2982	2563	2854	2563	2563

Case 10

	Control period					After frusemide							
Time (min)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min)	99	96	92	103	111	112	112	107	108	108	105	108	108
Pulmonary artery pressure (mmHg) systolic	38	—	40	48	49	46	41	35	38	37	35	36	37
diastolic	22	—	23	26	27	25	22	21	22	21	18	20	20
mean	28	—	29	34	35	33	29	27	28	27	26	27	27
Aortic pressure (mmHg) systolic	137	—	137	140	140	137	140	137	137	137	137	137	137
diastolic	97	—	100	100	100	103	103	100	100	97	100	100	100
mean	120	—	113	117	117	120	120	117	117	117	117	117	117
Pulse pressure (mmHg)	40	—	37	40	40	34	37	37	37	40	37	37	37
Cardiac output (l/min)	3.9	—	4.5	—	5.1	4.5	5	4.6	4.7	4.2	4.3	4.6	4.6
Stroke volume (ml)	39	—	49	—	46	40	46	43	44	39	41	43	43
Left ventricular work (kgm/min)	5.2	—	5.5	—	6.2	5.8	6.9	6.0	6.1	5.5	5.8	6.1	6.1
Left ventricular stroke work (Gm M)	52	—	60	—	56	52	61	56	57	51	55	57	57
Systemic resistance (dyn sec cm)	2459	—	1771	—	1558	2131	1844	2033	1989	1908	1870	1732	1732

Case 1

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	70	72	71	70	70	66	68	69	77	65	66	76	61
Pulmonary artery pressure (mmHg) systolic	34	32	33	41	41	37	37	35	33	30	31	33	36
diastolic	15	14	15	17	17	15	15	12	13	12	12	14	15
mean	22	21	4	26	—	23	23	20	20	19	19	21	23
Aortic pressure (mmHg) systolic	100	100	98	110	104	112	107	97	103	104	93	100	106
diastolic	55	55	53	60	59	60	61	55	59	59	50	60	69
mean	75	75	72	80	—	81	83	74	78	78	70	75	79
Pulse pressure (mmHg)	45	45	45	50	45	52	46	42	44	45	43	40	37
Cardiac output (l/min.)	—	5.9	6.3	6.0	—	5.4	5.2	5.4	5.5	5.3	5.4	6.0	5.7
Stroke volume (ml)	—	82	89	86	—	82	76	78	71	82	82	79	93
Left ventricular work (kgm/min.)	—	4.9	4.9	5.1	—	4.8	4.7	4.6	4.9	4.8	4.3	5.0	5.0
Left ventricular stroke work (Gm.M.)	—	68	69	74	—	74	69	66	63	4	65	66	76
Systemic resistance (dyn.sec.cm^{-5})	—	1016	913	1066	—	1199	1260	1095	1133	1176	1036	999	1108

Case 36

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	96	97	98	97	101	100	98	98	96	95	98	96	92
Pulmonary artery pressure (mmHg) systol	35	38	39	37	38	33	31	31	32	31	31	34	34
diastolic	16	16	17	16	18	0	15	13	15	14	11	16	14
mean	24	27	27	27	27	24	22	22	22	21	21	22	22
Aortic pressure (mmHg) systolic	132	130	132	137	—	135	133	133	135	132	13	12	128
diastolic	96	97	96	100	—	100	97	95	100	98	96	93	94
mean	111	110	113	116	—	117	113	113	113	113	111	107	111
Pulse pressure (mmHg)	36	33	36	37	—	38	36	38	33	34	36	34	31
Cardiac output (l/min.)	—	3.7	3.3	3.5	3.2	3.1	3.6	3.6	3.0	3.2	3.6	3.5	3.4
Stroke volume (ml)	—	38	34	36	32	31	37	37	31	34	37	36	37
Left ventricular work (kgm/min.)	—	4.7	4.3	[illegible]	—	4.1	4.8	4.9	4.0	4.3	4.9	4.3	4.5
Left ventricular stroke work (Gm.M.)	—	49	41	49	—	41	49	50	41	16	50	45	49
Systemic resistance (dyn sec cm⁻⁵)	—	2576	2737	2649	—	3016	2509	2509	3010	2822	2331	2443	2609

Case 40

	Control period					After frusemid							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	66	67	69	69	70	68	70	73	70	74	73	78	75
Pulmonary artery pressure (mmHg) systolic	31	30	33	35	34	29	26	6	26	25	24	26	24
diastolic	15	15	16	16	16	14	11	13	12	11	12	11	11
mean	21	22	24	24	24	20	18	18	18	17	17	17	16
Aortic pressure (mmHg) systolic	176	173	175	170	172	184	179	178	177	170	175	181	169
diastolic	94	90	98	93	90	98	96	97	95	94	90	95	92
mean	125	123	125	125	1 5	129	128	128	124	125	125	130	1 4
Pulse pressure (mmHg)	82	83	77	77	82	86	83	81	82	76	85	86	77
Cardiac output (l/min.)	4.0	—	4.0	4.2	—	3.7	4.1	3.7	4.3	4.1	1.4	5.1	4.1
Stroke volume (ml)	61	—	58	61	—	54	59	51	61	55	60	65	55
Left ventricular work (kgm/min.)	6.0	—	5.9	6.2	—	5.8	6.4	5.8	6.5	6.4	6.8	8.3	6.3
Left ventricular stroke work (Gm.M.)	91	—	86	90	—	84	91	80	93	85	92	105	85
Systemic resistance (dyn sec cm⁻⁵)	2498	—	2498	2379	—	2786	2495	2765	2305	2437	2270	2037	2417

Case 45

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	82	83	86	88	88	91	92	84	85	81	91	89	90
Pulmonary artery pressure (mmHg) systolic	41	46	47	51	48	46	43	33	29	31	30	21	21
diastolic	15	16	15	16	16	15	10	8	7	6	5	1	5
mean	25	27	28	30	30	27	22	15	15	15	12	8	10
Aortic pressure (mmHg) systolic	150	150	150	147	150	157	157	163	153	150	150	143	157
diastolic	8	87	87	90	87	93	93	93	90	87	83	87	97
mean	113	113	113	117	117	117	120	120	117	113	110	110	117
Pulse pressure (mmHg)	63	63	63	57	63	64	64	70	63	63	67	56	60
Cardiac output (l/min.)	4.8	4.	5.2	5.1	4.6	4.7	4.5	4.0	4.2	4.2	3.6	4.3	3.7
Stroke volume (ml)	59	54	60	58	52	52	49	48	49	52	40	48	41
Left ventricular work (kgm/min.)	6.5	5.9	6.9	7.0	6.3	6.6	6.7	6.1	6.3	6.1	5.1	6.2	5.6
Left ventricular stroke work (Gm.M.)	80	71	80	80	71	74	73	73	73	76	57	69	6.
Systemic resistance (dyn sec cm)	1881	2007	1737	1833	2033	1989	2131	2398	2226	2150	2442	2044	577

Case 49

	Control period					After frusemide							
Time (min.)	00	15	30	45	60	15	30	45	60	75	90	105	120
Heart rate (beats/min.)	87	88	87	86	88	88	93	88	89	94	86	86	90
Pulmonary artery pressure (mmHg) systolic	57	59	59	57	56	39	31	30	26	24	2	1	2
diastolic	16	17	17	18	17	17	12	10	11	9	8	7	8
mean	23	24	25	24	25	24	19	17	16	14	14	13	14
Aortic pressure (mmHg) systolic	186	184	182	182	187	188	187	180	176	166	168	163	160
diastolic	94	92	87	90	94	90	94	91	88	79	80	78	81
mean	130	131	128	128	133	130	134	130	124	117	119	116	114
Pulse pressure (mmHg)	92	92	95	92	95	98	93	89	88	87	88	85	79
Cardiac output (l/min.)	—	3.6	3.9	4.0	—	3.8	3.7	8	3.5	3.2	3.6	3.3	3.5
Stroke volume (ml)	—	41	45	47	—	43	40	32	39	34	42	38	39
Left ventricular work (kgm/min.)	—	5.6	5.9	6.0	—	5.8	6.1	4.6	5.4	4.	5.4	4.9	5.0
Left ventricular stroke work (Gm.M.)	—	64	68	70	—	66	66	52	60	50	63	56	56
Systemic resistance (dyn sec m⁻⁵)	—	2908	2625	2557	—	2734	2894	3711	831	29 2	2642	2809	2603

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CORONARY HEART DISEASE IN MALE TWINS

Hereditary and environmental factors in concordant and discordant pairs

By Ingvar Liljefors

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ERRATA

Page	Col	Line	Read
11	2	7	& Kunkel *have* demonstrated the role of phospho-
		25	Using an electrophoretic technique *Fredrickson* &
14	2	35	in its most marked *form* as particularly predictive
22	2	24	(Fig. 2) The DZ and XZ pairs numbered 904,
28	1	16	systems ABO MN P K, *Le Fy* Jk and Rh
39	2	3 4	twins with angina pectoris *or suspected angina* recorded S-T changes of the ischaemic type (S-T 1—4) during exercise
41	1	21	examined pairs comprising the final material 57
69	footnote missing		footnote on page 70

39 Table 19

TABLE 19 Abnormal Q-waves or S-T depression in twins performing the exercise test

	N	Q 1 2 or S-T 1—4 during exercise No	%	Q 3 or S-T 1—4 after exercise[a] No	%	Subjects on digitalis included
CHD symptom						
Infarction[b]	18	14	78	1	6	4
Angina pectoris[c]	29	20	69	5	17	5
Suspected angina	23	9	39	1	4	2
No such symptoms	94	17	18	14	15	4

[a]In subjects without Q 1 2 and S-T 1—4 *during* exercise

[b]With or without angina pectoris

[c]Including 2 subjects with suspected infarction

[d]Including 1 subject

CORONARY HEART DISEASE IN MALE TWINS

From the Departments of Medicine and Clinical Physiology
Karolinska Institutet at Serafimerlasarettet the Department of Environmental Hygiene
Karolinska Institutet and the National Institute of Public Health Stockholm Sweden

CORONARY HEART DISEASE IN MALE TWINS

Hereditary and environmental factors in concordant and discordant pairs

By

INGVAR LILJEFORS

STOCKHOLM 1970

Translated from the Swedish

by

VICTOR BRAXTON

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Preface

Research in the field of preventive medicine is greatly hampered by deficient knowledge of those conditions in man's environment that may be responsible for diseases and their sequelae and this is particularly true of arteriosclerotic heart disease. In our approach to the aetiology of this disease the analysis of factors of an environmental nature must therefore receive some degree of priority. The initial problem, namely that of distinguishing environmental from genetic traits, is a complex one. For example, a certain trait may run in families, thereby resembling inheritance, or a person's choice of a particular environment can be governed by heredity. Materials where the effect of genetic factors can be eliminated offer the requisite conditions for ascertaining which environmental factors are associated with manifestations of a particular disease. Such a material is provided by the register of like-sexed twin pairs that has been compiled in Sweden for the prime purpose of examining factors of aetiologic importance for diseases of the respiratory and cardiovascular system. The material for the present investigation was obtained from this twin register.

The study constitutes an item in the programme of research on the causes of coronary heart disease that is being conducted at the Departments of Medicine and Clinical Physiology at the Serafimer Hospital and the Department of Environmental Hygiene of the Karolinska Institute and the National Institute of Public Health, Stockholm. Of 91 male sets of twins aged between 42 and 67 years that were selected by means of mailed questionnaires for clinical examination 60 contained at least one member with signs and symptoms of coronary heart disease. The investigation was undertaken to ascertain the significance of heredity and environment for various manifestations of coronary heart disease in men of working age by analysis in these twins of those factors considered to be associated with the disease. The investigation is a retrospective one and, as such, open to criticism on several points. However, as no retrospective epidemiologic studies on twins have apparently been performed in this field, it was considered that such an investigation of the Swedish twin material must be rewarding if only by virtue of the possibility it provides for separate analysis of genetic and environmental factors.

An investigation such as the present one must inevitably rely on the concerted efforts of many parties. The examinations and the interviews of the twins were performed at the Department of Medicine, Serafimer Hospital, whose head, Professor Gunnar Biörck, M.D., initiated my interest in this line of research, and at the Department of Clinical Physiology, the head of which, Bengt Persson, M.D., kindly assisted in the interpretation of the electrocardiograms. The Swedish Twin Register, which, as mentioned above, was the source of the material for this investigation, was compiled under the guidance of Professor Lars Friberg, M.D.; his advice on its analysis is gratefully acknowledged. Part of the statistical analysis of the results was carried out at the Department of Sociology of the National Institute of Public Health under the supervision of Rune Cederlöf, Ph. D., together with his collaborators Miss Birgitta Flodérus, fil. kand., and Kenneth Berglund, fil. kand. Professor Erik Lindgren, M.D., head of the Department of Radiology, Serafimer Hospital, placed personnel and laboratory facilities at my disposal. The heart volume determinations were carried out by Arne Ryttman, M.D. The chemical analyses were performed at the Department of Clinical Chemistry, Serafimer Hospital, and supervised by Rolf Blomstrand, M.D. To the planning work and the selection of the material Ove Carlson, M.D., fil. kand.,

made an important contribution and also carried out the interviews concerning the environmental conditions of the twins. The diet interviews and food analyses were performed by Mrs Ingrid Mjöberg, together with Miss Ingrid Ekengren at the Department of Medicine, Serafimer Hospital. Valuable assistence in the clinical examinations has been provided by Miss Eva Bonde, Mrs Kerstin Elfström and Mrs Gertrud Degerstedt.

The electrocardiograph and the bicycle ergometer used in the examinations outside the Serafimer Hospital were kindly placed at my disposal by Elema-Schönander AB and Monark Crescent AB, Stockholm.

For much of my knowledge of twin studies I am indebted to Torbjörn Lundman, M.D. The collation of the results was scrutinized by among others, Erik Orinius, M.D. whose constructive criticism is much appreciated. Mrs Viveca Hultén, who drew the figures has, with Mrs Gunilla Haag, assisted with secreterial work.

To all these and the many others that in various ways have contributed to the investigation I wish to extent my warm thanks—and likewise to my wife, Mrs Bodil Liljefors who not only helped with the collection of the present twin material but also made possible a prospective study of male twins in our own family.

Grants for this research received from the above institutions and the Swedish National Association against Heart and Chest Diseases are gratefully acknowledged.

STOCKHOLM *April 1970* *INGVAR LILJEFORS*

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Introduction

Coronary heart disease (CHD) is being diagnosed to an increasing extent among the populations of the advanced countries and vigorous efforts are being made throughout the world to solve the problems associated with the causation of this disease and to check the upward trend of the morbidity curve by instituting preventive measures[204]. In the adult CHD is largely synonymous with coronary arteriosclerosis[87].

Clinical manifestations of CHD are not always accompanied by histologically demonstrable changes in the coronary vessels, and *vice versa*[87]. The fact that the clinical picture of CHD thus does not always reflect the true extent of the vascular changes complicates the evaluation in the individual case. The fundamental causes of these differences in clinical manifestations are still obscure.

FACTORS ASSOCIATED WITH CORONARY HEART DISEASE

Our knowledge of the aetiology of CHD has been obtained in various ways. Retrospective studies of materials in which a comparison has been made between persons with and without overt CHD have brought to light certain factors that are associated with this disease, and some of these have been shown in animal experiments to be correlated with the presence of arteriosclerotic changes. In prospective studies a number of the factors associated with CHD have been examined with respect to the occurrence of overt CHD in persons originally without manifestations of the disease. In a system where several factors may be acting and perhaps also co-varying, difficulties arise in isolating the individual factors of causal importance. Retrospective studies are usually performed in clinical case series comprising selected groups, whereas epidemiologic investigations of both retrospective and prospective types require large populations that will provide a material which can be meaningfully analysed.

The factors found to be associated with CHD may be of the nature either of biometric variables measured or detected in the individual, or of environmental exposure. These 2 types of factors might conveniently be designated *intrinsic* and *extrinsic* factors (Fig. 1). Many of the former are probably governed by heredity but might also be influenced by the environment. Extrinsic factors may be of the nature of habits closely linked to the genetic constitution and usually developed in the family, which constitutes the immediate environment, or they may represent the remote environment to which the individual can be exposed by chance or by self selection[21, 25].

Factors found to be associated with the occurrence of CHD may be causal either in that they are predisposing for the disease or that they precipitate it[25]; some factors might possibly be non-causally associated with CHD through co-variation with causal factors. These factors of risk have been the subject of a number of comprehensive surveys of the literature[86, 63, 90, 116, 180] and it will suffice here to outline the ones examined in the present investigation.

Intrinsic factors

BODY BUILD

An investigation carried out by Dublin[63] of the Metropolitan Life Insurance Company disclosed an increase in mortality with overweight. This

farction was 33 years, and on registration a systolic pressure of at least 140 mmHg was recorded in 28 per cent, aginst 9 per cent for a control group. A diastolic pressure of more than 90 mmHg was recorded in 19 per cent of the infarction group against 4 per cent of the controls.

In Paffenbarger's study[140] on students dying from CHD their blood pressure at 20 years of age was higher than for the control group. From the Framingham study[110] it would appear that an elevated blood pressure implies an increased risk of developing clinical signs of CHD for the men, however the risk of angina pectoris only seemed to be less than that of infarction. In the Tecumseh population study[76] elevated blood pressure in men was found to be significantly associated with CHD but not manifested as angina pectoris or ECG evidence alone or combined. On the other hand in the Los Angeles Heart Study[83] blood pressure elevation was more often associated with angina pectoris unaccompanied by known infarction; similar results were obtained in a prospective study of 50-year-old men in Göteborg[190].

Studies on laboratory animals and retrospective and prospective investigations on man have thus shown that the elevation of the blood pressure is associated with a greater risk of clinical CHD but in respect of the 2 forms of manifestations, infarction and angina pectoris, the results are inconsistent.

SERUM LIPIDS

Cholesterol was found by Aschoff[10] to be one of the main constituents of atheromatous vascular changes. It was consequently not long before the problem of arteriosclerosis, and hence of CHD came to be centred primarily on the cholesterol content of the circulating blood. In laboratory animals atheromatous has been produced by increasing the serum cholesterol level[8, 130]. In clinical case series an elevated cholesterol level has been found in a greater proportion of cases of CHD than the normal population[22, 42, 74, 88, 182, 197]. The part played by an elevated cholesterol level as a risk factor in the development of overt CHD has been confirmed by prospective studies[76, 109, 168, 180]. The Los Angeles Heart Study[83] showed a stronger correlation of cholesterol level with infarction than with angina pectoris, a result similar to that found in the Göteborg study[190].

The aetiologic significance of other lipid fractions for CHD has also been investigated. Ahrens & Kunkel[6] has demonstrated the role of phospholipids as a stabilizer for the cholesterol fraction, and a high cholesterol value in relation to the phospholipid level was considered to favour the development of atheromatosis. The triglyceride level has been shown by Albrink & Man[8] to be correlated with the presence of CHD. Dividing the lipid-bearing proteins according to density—high, low and very low—by ultracentrifugation, Gofman and collaborators[80] found a closer correlation with CHD for the very low than the low density fractions. On the basis of these observations Carlson[43] performed a study of men aged 33—65 surviving infarction. Their triglyceride level was higher than for a control group but the difference was significant only for those of 50 year or less. Above this age the elevation of the cholesterol was more marked.

Using an electrophoretic technique Fredrikson & Lees[73] separated the lipid-bearing proteins and proposed a division of the lipid disorders into 5 main types, 3 of which (II—IV) were found to exert a distinct atherogenic effect. Type II was characterized by essential hypercholesterolaemia, and types III and IV also by a rise in the triglycerid concentration. The last 2 types were usually characterized also by a disturbance of the glucose tolerance and could be induced by high carbohydrate intake. The electrophoretic separation of the lipoproteins would seem to offer a simpler method of detecting persons prone to CHD than does ultracentrifugation.

URIC ACID

The relation between gout and the manifestations of arteriosclerotic disease was mentioned 1897 by Osler in *"The principles and Practice of Medicine"*. Attacks of gout would sometimes seem to occur in connection with infarction, as has been pointed out by Ask Upmark & Adner[11]. From the

results of earlier studies Hansen[86] found support for the view of a relationship between gout and arteriosclerotic disorders. The group of 94 young men with recorded infarction studied by Gertler & White[86] had a significantly higher mean uric acid concentration in serum than the controls matched with respect to among other things, body build In the Tecumseh population Myers *et al*[141] found a significantly higher mean for the men with symptoms of CHD than for other men when account was taken of age and relative weight They pointed out, however that in a number of other studies the results are conflicting.

Should there be a causal connection between CHD and uric acid level the mechanism remains to be established Gertler and co-workers[85] proposed that the uric acid promotes deposition of cholesterol in the vessel wall. There is no consistent evidence of a correlation between the uric acid and the lipid content of the serum.

The uric acid concentration would seem, according to Rahe *et al*[157] to vary with conditions involving mental stress. Montoye *et al*[130] found a significantly higher mean level in a group of business executives in the Tecumseh population than in the rest of the males examined. The uric acid concentration was positively correlated with weight but not with skin fold thickness. That a male body build is characterized by a higher uric acid level more than is adiposity has also been asserted by Gertler & White[86] and Benedek[19]

The basis for the view that gout and hyperuricaemia have a hereditary origin has been examined by Smyth[177] Any association between the uric acid concentration and CHD may thus be of a hereditary nature It cannot, however, be excluded that an elevated level may be a manifestation of an exogenous causal factor From the results presented to date it cannot be judged whether the observed associations are of a causal type

DIABETES MELLITUS

Persons with overt diabetes mellitus are affected to a greater extent than others by arteriosclerotic diseases, including CHD[15, 183] Conversely diabetics have been found to be overrepresented among those with CHD[173, 183] Diabetes mellitus is accompanied by disturbance of the lipid as well as the carbohydrate metabolism[100] Gofman[89] among others has maintained that the excess morbidity from CHD among diabetics is due chiefly to an increase in the atherogenic lipoprotein fractions.

It has, however been confirmed in several investigations—reviewed by Epstein[71]—that lowered glucose tolerance occurs frequently in patients with arteriosclerosis. Wahlberg[186] examined a series of 530 patients with no endocrinal disease but with ischaemic manifestations 330 of whom had a history of infarction. Of those with ischaemic disease 44 per cent had a normal glucose tolerance after intravenous load against 86 per cent of the controls Among the men of this series he found no correlation between the glucose tolerance (the *K* value) and elevated cholesterol or triglyceride levels The Tecumseh population study[143] showed that of the men over 40 years that had demonstrable CHD 37 5 per cent had overt diabetes or an elevated blood glucose level one hour after peroral load. At the follow-up examination the reduced glucose tolerance in the population at risk seemed to be associated with the incidence of fatal CHD[70]

Diabetes mellitus may have a bearing on the development of CHD through the elevation of certain lipid fractions[100] but reduced glucose tolerance must be regarded as a likely risk factor *per se* even though few definitive results of prospective studies are available.

Extrinsic factors

DIET

The results of studies on laboratory animals[8, 120] and of the prevalence of arteriosclerosis in populations with different dietary patterns[119, 120] point to the diet as being of probable aetiologic importance for CHD Overeating, and resulting overweight, would seem to be less important in this respect than the type of food[117] There is convincing evidence that a high animal fat content—except those of marine origin—produces a higher concentration of certain lipid fractions than an iso-

caloric diet in which the animal fats have been replaced by vegetable fats[35, 90] A reduction in fats and caloric content may lower the cholesterol level[118] whereas replacement of fats with carbohydrates in some cases produces a rise in other lipids, especially triglycerides[7]

In the Coronary Prevention Evaluation Programme[181] started in 1957 the effect of an alteration of risk factors on the occurrence of CHD was examined in a cohort of some 500 men aged 40—59 initially without symptoms of CHD the men were selected for the Programme on the basis of the presence of one or more risk factors, namely hypercholesterolaemia, obesity hypertension, cigarette smoking and physical inactivity Prevention was based essentially on nutritional measures. Comparison with a control group indicated promising results of correction of serum lipids, blood pressure and overweight. Deaths from CHD tended to be fewer than for the drop-outs, but the numbers were too small to permit of statistical analysis A number of other studies of primary and secondary prevention, reviewed by Stamler[181] point to a beneficial effect of a dietary regimen as regards the prevention of the occurrence or relapse of CHD The fact that insufficient account has been taken of the effects of a particular diet on the various lipoprotein patterns, as classed by Fredrickson[78] may be one reason why some of the prevention trials reported to date have not conclusively demonstrated the value of the methods used[64, 122, 139] One difficulty of examining the effect of changing the diet as measure of primary prevention is non-adherence, for this might result in selection of subjects differently predisposed to CHD from those able to adopt a prudent diet.

Although a significant change in the dietary pattern may diminish the risk of CHD in susceptible persons, it is still uncertain whether the average diet typical of the industrialized societies is responsible in some measure for the high CHD morbidity rates in these countries Within such populations the fat intake of persons with established CHD has not been found to be higher than for the population at large[30, 72, 181, 210] According to Fredrickson[78] the various lipoprotein patterns are differently affected by diet, a fact that should be taken into account in any appraisal of the possible aetiologic importance of diet for CHD

SMOKING

The statistical relationship between cigarette smoking and the excess mortality from CHD is convincing. However in *Smoking and Health* a survey and analysis of the research on the effects of smoking published in 1964 by the Surgeon General's Advice Committee on Smoking and Health in the United States[193] no causal nature of the relationship was established. The numerous reports concerning the relationship between smoking and CHD that have since accumulated have been reviewed in *The Health Consequences of Smoking*"[194] issued in 1967 and supplemented in 1968 According to this report it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease This conclusion is based on the additional epidemiologic evidence of higher CHD morbidity rates for smokers than non-smokers, and the results of current physiologic research that indicate biomechanisms whereby smoking might be contributory cause of the disease

The fact that the prospective studies[184, 199] have disclosed stronger correlation of cigarette smoking with fatal manifestations of CHD than with the milder ones has drawn attention to the possible *acute effects* of the habit. Among the mechanisms proposed are an increase in cardiac output creating a great oxygen demand in the myocardium[115] and induction of arrhytmias[190] Another possible explanation of the alleged acute effects is the impairment of th oxygen supply to the myocardium—particularly in the case of inhaling, heavy smokers[14]

The *chronic effects* of smoking would seem to be more obscure, since some prospective studies[21, 199] have indicated that the risk of CHD is independent of the duration of smoking Evidence of a chronic effect is found the excess morbidity of angina pectoris unaccompanied by infarction observed in the Health Insurance Plan Study[171]

and the greater severity of histologically confirmed arteriosclerosis in smokers than non-smokers[16, 207]. In experiments in laboratory animals Astrup, Kjeldsen & Wanstrup[15] found that vascular atheromatosis was accelerated by a carbon monoxide content of the blood approximately equal to that in smokers with ischaemic disease.

In most investigations quoted in the 1968 Supplemental Report smoking was observed to be associated with CHD independently of other factors, but when combined with such factors the risk was considerably greater. These results are supported by the prospective study of men in Göteborg born in 1913[190]. The results of conventional epidemiologic investigations do not, however, assert a causal connection with CHD. As smokers comprise a self-selected group other factors might be involved that do have a causal relationship with CHD. Twin studies in Sweden[65] and the United States[81] have disclosed an excess prevalence of CHD symptoms in smokers when genetic factors were not kept under control; however, when genetic differences between the smokers and non-smokers were eliminated by performing comparisons within smoking-discordant sets of twins, this excess prevalence was no longer apparent.

PHYSICAL ACTIVITY

In experiments on laboratory animals attempts have been made to stimulate atherogenesis by reducing physical activity, but the results have been contradictory[114]. In retrospective clinical studies physical inactivity has been found to be characteristic of patients with CHD[60, 112, 127]. Whereas the risk of infarction has been found to be negatively correlated with physical activity in the Framingham and Health Insurance Plan studies[169, 171], a positive relationship was observed in the latter for angina pectoris. In both these studies, moreover, the *mortality* was greater for the sedentary groups, and herein may lie one reason why in some retrospective studies[74, 168, 197] no correlation has been found between physical inactivity and CHD in survivors.

Other prospective studies[3, 84, 111, 131] have disclosed no relationship between physical inactivity and CHD. In a review Fox & Haskell[75] state that physically active persons have less CHD but the influence of physical activity appears to be more striking on myocardial infarction, scars, and fibrous patches than on the atherosclerotic process. They suggest, however, that "the benefits of activity may result in part from the stimulus toward more prudent behavior relative to smoking, weight control, coffee consumption and, perhaps, even the manner in which we are able to handle the stress and strain of life".

PSYCHO-SOCIAL FACTORS

According to Morris[127] the increasing prevalence of CHD in the Western countries appears not to be accompanied by an increase in the frequency of atheromatosis. This has focused interest on certain precipitating factors in the environment characteristic of the industrialized society. Less clearly definable than, for instance, cigarette smoking, excessive consumption of animal fats or physical inactivity are the psycho-social factors.

It has long been considered that persons with infarction tend to belong to a certain personality type[148]; van der Valk & Groen[196] call them "work addicts". Prospective studies by Ostfeldt *et al*[147] and Rosenman & Friedman[166] also indicate that a certain behaviour pattern predisposes for the development of CHD. The latter workers distinguish what they term "behaviour pattern A", characterized by excessive drive, aggressiveness, ambition, competitiveness and a profound sense of time urgency; there are also certain motoric traits such as forceful, rather rapid speech accompanied by sudden gestures[51]. They see this behaviour pattern in its most marked form as particularly predictive for the development of overt CHD, and independent of other risk factors. According to Ostfeldt the risk of infarction and of angina pectoris alone are associated with different emotional behaviour patterns.

Has this behaviour only a genetic origin or may external factors contribute? Rosenman[167] stresses that type A is an interplay of certain personality (endogenous) and environmental (exogenous) factors. It exists particularly in the milieu that

characterizes our modern urban civilization Studies by Pearson & Joseph[152] Russek & Zohman[168] and Weiss[200] point to the occurrence of more severe and more frequent emotional stress in persons with infarction than in normals.

That certain specific environmental factors such as changes in the type of residential and working environment and social group characterize persons with CHD has been shown by for instance, Syme[186] Tyroler & Cassel[191] and Wardwell[196] It was found by Wolf and his colleagues[78] In the case of Roseto—a district in the United States with a *high proportion of Italian immigrants that has* retained its sociocultural pattern—that the incidence of fatal myocardial infarction was lower than in the surrounding region. The authors conclusion that the lower CHD rate could be attributed to a greater stability of community has however been criticized by Keys[120]

Several studies—extensively reviewed by Marks[132]—have dealt with occupation in relation to CHD Among 264 occupationally active men hospitalized for primary infarction between 1950 and 1954 Biörck, Blomqvist & Sievers[22] found a significantly greater proportion of employers than clerks and workers. Most of them were people who had fought their way up and continued to work hard for their living in small enterprises. A study of CHD by Morris *et al*[134] in British physicians has focused interest on working intensity as a risk factor in particular occupational category It was found by Buell & Breslow[30] that the risk of fatal myocardial infarction increased with the amount of overtime work.

A lower CHD prevalence for the better educated employees of the Bell system, Hinkle *et al*[100] interpreted as indicating a constitutional selection, since differences were also found in for instance, body build and smoking habits.

Emotional stress has been shown by several authors to produce an increase in the level of lipids correlated with CHD[45, 64, 80, 82, 83, 157] In the "Stockholm Prospective Study by Carlson & Lindstedt[43] the initial examination disclosed higher triglycerid levels in healthy men in supervisory than in subordinate positions up to about 50 years of age. Moreover in studies of physiologic and psychologic reactions under emotional stress reported at an international symposium held in 1967 a number of such reactions were considered to have a causal relationship with CHD[123]

Importance of heredity

It has frequently been found in clinical studies that the families of cases of CHD commonly contain a history of this disease[96, 121, 143, 170, 203] It should be borne in mind however that in retrospective studies persons with *CHD* are more likely to be aware of members of the family with similar symptoms than are unaffected persons. In a study carried out by Slack & Evans[175] the effect of this source of error appears to have been diminished for the first degree relatives of some 200 men and women with CHD aged less than 60 and 70 years, respectively the risk of dying from CHD was compared with that for relatives of a control group For the male relatives of the *men* contracting CHD before 55 years the risk of dying from CHD before the same age was 5 times greater than expected. For the femal relatives of the men the risk was only 2½ times as great. For both male and female relatives of the *women* contracting CHD before 65 years the risk of dying from CHD before 55 and 65 years, respectively was about 7 times greater than expected. For the relatives of the CHD cases contracting the disease at 65 years or later the risk was increased little, if at all Regarding the purely genetic causal component f CHD the authors express themselves *with reserve. Many important environmental fac*tors are common to near relatives In the prospective Tecumseh population study[76] a greater incidence of CHD than in the same number of controls was recorded only for female relatives of the 209 persons that initially had the disease.

In the case of the individual factors associated with CHD there is ample evidence of a hereditary component in the aetiology An example is provided by essential hypercholesterolaemia[140] which is considered by Wilkinson *et al*[208] Adlersberg *et al*[4] and Svendsen[184] to have an incompletely

dominant mode of transmission with a higher cholesterol level and the occurrence of xanthoma in the homozygotes and only moderately elevated values for heterozygotes. This disease is associated with a high excess mortality from CHD especially at an early age. It was also found by Slack[176] that CHD and a fatal outcome from this disease were more common in 44 patients with hypercholesterolaemia—Fredrickson's type II hyperbetalipoproteinaemia—than in 34 patients with hyperlipoprotein patterns of types III—V which grouping included elevated triglyceride levels. For 60 relatives of the former group found to have the same lipid pattern as the 44 patients of this group the manifestations of CHD were earlier and more severe than for the 7 relatives of the latter group affected by the same lipid disturbance as the 34 patients. In connection with an earlier study it was suggested that type II hyperbetalipoproteinaemia is inherited through a single autosomal dominant gene but for lipoprotein pattern types III—V which constitute a fairly heterogenous entity the heredity might be multifactorial.

The inheritance of high blood pressure was found by Pickering[164] to be polygenic, but, as pointed out by Miall & Oldham[135] the genetic resemblance of first degree relatives leaves between 55 and 77 per cent of the systolic variance and between 70 and 87 per cent of the diastolic variance to be accounted for by environmental factors.

Gout is a disease that often displays a familial occurrence. It has been shown by Smyth[177] and Hauge & Harvald[86] that hyperuricaemia occurs more often than expected in relatives of patients with gout. The latter authors found that the uric acid level occurred as a continuous variable and concluded it must be dependent on more than one abnormal gene.

Although diabetes mellitus would seem to be due in some measure to hereditary factors, there is no proof that the familial occurrence of diabetes predisposes for the development of CHD[88, 196]. The Tecumseh study[89] however disclosed a familial similarity in respect of the parameters cholesterol, blood pressure, weight and glucose-induced blood sugar level.

Thomas & Cohen[188] found that CHD was 4 times more common among persons whose parents had CHD than among persons outside the family. They inferred that the aetiology is dependent on multiple genetic factors modified by the effect of environment. In a study of various factors associated with CHD Thomas[189] found a correlation with the familial occurrence of this disease and hypertension. It is of interest to note that smoking was numbered among these factors.

Because of the multifactorial causation of CHD the average importance of genetic factors as a whole is difficult to assess. The Framingham and Göteborg investigations[109, 190] suggest that certain factors cumulatively increase the risk of CHD. The hereditary influence would seem, moreover to vary with age and sex. Twin studies afford the opportunity of isolating the effects of heredity and environment.

TWIN STUDIES

Twin methods

Because of the identical genetic constitution in monozygotic twins (MZ) and the less similar one in dizygotic twins (DZ) twin studies are useful for examining the influence of heredity on the occurrence of certain traits and effects. Reviews on the earlier literature on twin studies have been published by among others, Dahlberg[44] and Gedda[84]. Basic principles for the use of twins in epidemiologic studies have been presented in a report of a WHO meeting of investigators[205].

For ascertaining the significance of genetic factors for certain traits where the influence of environment is judged to be comparatively small, one may compare the *concordance* with respect to certain traits in MZ and DZ pairs this provides, how

ever an unbiased selection of pairs moreover it assumes that intra pair differences in the influence of environment are of roughly the same magnitude for MZ and DZ pairs, and this is not necessarily the case the consequent error in this twin method will then increase with the importance of environmental factors for the trait in question. Another type of error may arise if the trait is one due to dominant genes with low penetrance the concordance may then be wrongly assessed especially when the series is small. A variable expressivity of a gene will result in a variable intensity of the trait in question, and this, too, may lead to difficulty in determining the concordance. Comparison of the concordance in MZ and DZ pairs as a method to determine the influence of heredity must therefore be applied with reserve.

The importance of genetic factors may also be elucidated by estimating the *coincidence* of a certain trait. The expected coincidence, calculated from the prevalence of the trait in the material, is compared with the observed coincidence—the proportion of concordant pairs in the twin series

The importance of heredity for traits having the nature of continuous variables may be examined by means of intra-pair comparisons A smaller difference between partners of MZ than DZ pairs indicates that the trait is dependent more on genetic than environmental factors.

Finally these twin methods are of value only for examining the relative importance of genetic factors. In what way a certain trait is inherited can be ascertained only from pedigrees.

More appropriate from the medical aspects is the co-twin control method introduced by Gesell[87] This is suitable for studies of the effects presumably d e to environmental factors, where it is desired to eliminate the influence of heredity Such study can be performed retrospectively and then twin pairs where the co-twins are known to have been differently exposed to the environmental factor in question are examined for the expected effect. A prospective study is performed in the same way by comparing the effect in the exposed and unexposed members of pairs. A variant of this method is to ascertain the difference in exposure for the environmental factor in twin pairs differing (discordant) as regards a particular trait. Shortcomings of this method include the difficulty of establishing exposure to environment retrospectively This is particularly troublesome in cases in which the trait in question might be considered to develop over a fairly long period There is then a risk that the environmental exposure examined is parallel to or even a consequence of the trait itself

Twin methods for examining the importance of environmental influences are especially suitable when a certain trait is thought to be governed by both genetic and environmental factors, for by restricting the study to monozygotic pairs the genetic factors are kept entirely under control. Traits due *chiefly to environmental factors* are not so suitable for twin studies.

Coronary heart disease in twins

CHD belongs to the group of diseases that apparently have a both hereditary and environmental aetiology From what has been said above it is evident that as regards the significance of heredity the results of studies of CHD concordance should be interpreted with reserve. The hereditary factors of importance for CHD presumably involve genes with incomplete penetrance or variable expressivity[59] The influence of environment, which is assumed to be relatively important, might be considered to be nearly more equal for twins of MZ pairs than of DZ pairs

The literature contains numerous case reports concerning concordance of CHD in twins[20, 62, 80, 100, 150, 172] A somewhat more systematic study of CHD concordance has been carried out by Kahler & Weber[108] who, among hospital cases of coronary disease found 17 twin pairs containing at least one twin who had symptoms of CHD Both twins of 3 of the 4 MZ pairs had CHD but none had verified infarction Of the 13 DZ pairs 6 like-sexed were male, and 2 of these were CHD-concordant in one of these 6 pairs one twin had had infarction and the other had no demonstrable CHD Two like-sexed DZ pairs were female in

one of them one twin had had infarction and the co-twin probably had CHD. The study of the twins was not uniform as regards either resting or exercise ECGs.

Epidemiologic studies of twin populations have been carried out in Denmark and Sweden, where registers have been compiled of all the pairs where both partners had reached certain ages.

The Danish register, which has been described by Hauge *et al*[90], comprises twins born in Denmark between 1870 and 1910. This material has been examined retrospectively and information relating to medical and social conditions has been obtained for about 8000 pairs reaching 6 years of age by means of questionnaires and from hospital records and autopsy reports. According to a recent report[97] the concordance rate for deaths from myocardial infarction was higher for the MZ than DZ pairs; for the male pairs however the difference was not significant.

At the Department of Environmental Hygiene, Karolinska Institute and the National Institute of Public Health a register of all like sexed twin pairs born in Sweden between 1886 and 1925 was compiled in 1959—61. To 11 000 of the 13 000 pairs both twins of which were living and resident in Sweden at the time the register was compiled questionnaires relating to medical and sociologic conditions were sent. This Twin Register and the results of the first questionnaire studies have been described by Cederlöf, Friberg and others[47, 48].

The questionnaire included questions concerning angina pectoris. Of the roughly 2250 MZ pairs and 3600 DZ pairs in which both twins had similar smoking habits significantly more MZ than DZ were concordant with respect to angina pectoris[49]. The excess concordance for MZ was, however, restricted to the women and to the men over 60 years of age.

To investigate the effect of smoking by the co-twin control method Lundman[126] examined a material of about 200 smoking-discordant twin pairs from the Swedish Twin Register, about one half of whom were MZ; he found a significantly higher coincidence of clinical or ECG signs of CHD than would be expected from the prevalence of such manifestations. For the DZ pairs the observed coincidence was not significantly greater than expected. The material displayed no differences between smokers and non-smokers in respect of these manifestations of CHD.

Factors associated with coronary heart disease

ANTHROPOMETRIC FACTORS

In a study of male twins aged 30—40 years, 75 of them MZ and 84 DZ, Takkunen[186] found that skeletal dimensions were chiefly influenced by heredity. Skin-fold thickness as a measure of adiposity appeared to be governed chiefly by environmental factors. The muscle factor, as expressed by the upper arm diameter, tended to be genetically determined.

BLOOD PRESSURE

In a collation of various twin studies on hypertension von Verschuer[201] found that 53 per cent of all the reported MZ pairs were concordant with respect to this property, against 22 per cent of the DZ pairs. Of Hines[102] 17 pairs 14 were MZ; in 8 of these both members had hypertension; 5 of these 8 pairs were male and the hypertension varied in degree. In a further 200 pairs examined, most of them below 25 years, the intra-pair difference in both systolic and diastolic pressures was smaller for the MZ than the DZ. In a study of 53 twins, most of them less than 30 years of age, Mathers, Osborne & de George[133] found a significantly greater inter- than intra-pair difference only for the females. Between female MZ and DZ pairs there was also a significant variation in the intra-pair difference. The dependence of blood pressure on genetic factors was greater in younger than older persons, and then especially in women. In his study of male twins Takkunen[186] found a greater intra-pair difference for DZ than MZ pairs; it was statistically significant only for the systolic pressure. Twenty-six pairs had been excluded because of various pathologic conditions; in 8 of these there was elevated blood pressure—defined as diastolic pressure in excess of 90

mmHg 6 of the pairs were MZ and 2 DZ and in one MZ and one DZ pair the elevation was concordant. In a study of 81 younger twin pairs Downie *et al*[63] found no significant difference between MZ and DZ in respect of the intra-pair variation. In his investigation of smoking-discordant twins Lundman[129] found a significantly greater intra-pair difference for the DZ pairs. As regards both systolic and diastolic pressure the level of significance was considerably lower for the male than female pairs.

To judge from the reported twin studies the blood pressure would thus seem to be in some measure under genetic influence, with reservation for the results for the younger men. An increasing intra pair similarity with age may be due to a diminishing influence of environment in favour of the genetic factors. This would be consistent with the results of a study of siblings in the Tecumseh investigation[90]

SERUM LIPIDS

In a study of 100 twin pairs less than 20 years of age, one half of them MZ, Gedda & Poggi[83] found that the cholesterol level was strongly dependent on genetic factors. Similar results have been reported by McDonough[60] for his study of 56 sets of twins in Georgia this material contained a greater proportion of older pairs than that of Gedda & Poggi In studies of the cholesterol by Osborne *et al* [145] Meyer[134] Jensen *et al*[106] and Rifkind *et al* [180] the intra pair differences were greater for the pairs living apart than for those living together this indicates an influence of environment on this property The intra-pair difference was, however, significantly greater for the DZ than the MZ co-habiting pairs. Lundman[129] found that the intra-pair difference in cholesterol was not significantly greater for the DZ than the MZ pairs as regards the phospholipid and triglyceride levels, however significant such differences were obtained for the female pairs. Jensen s[106] results, too, point to a genetic influence on these 2 lipid fractions, whereas Rifkind *et al*[180] found a significant difference as regard the beta lipoprotein and phospholipid levels only for the twins living apart. As these were older than those living together, just as in the investigations by Osborne[145] Jensen[105] and Meyer[134] it was inferred that the environmental influence might decrease with age.

URIC ACID

In Jensen s study[105] of 44 twin pairs the intra pair difference in uric acid level was smaller for the 27 MZ pairs than for the DZ. However significant differences were recorded also in the comparison between the MZ and DZ twins living together and those living apart. The uric acid level, too, thus appears to be influenced by both genetic and environmental factors.

DIABETES MELLITUS

In 131 twin pairs Then Berg[187] found concordance with respect to diabetes mellitus in 17 out of 46 MZ and 9 out of 83 DZ, including 41 unlike-sexed pairs. Harvald & Hauge[98] reported concordance in 47 4 per cent of 76 MZ pairs and 9 3 per cent of 238 DZ pairs. At the Joslin Clinic, White[197] found 16 out of 33 MZ pairs to be concordant with respect to overt diabetes, against 2 out of 63 DZ pairs. The corresponding figures obtained by Gottlieb & Root[81] at the same Clinic were 9 out of 30 MZ and 2 out of 60 DZ pairs. The difference was greater over 40 years of age. In 47 of the pairs examined by the oral glucose tolerance test, this was abnormal in both twins as often in DZ as MZ pairs. When overt and chemical diabetes were combined, 9 out of 21 MZ were concordant against 9 out of 26 DZ. Cerasi & Luft[83] however found that monozygotic twins in pairs discordant for diabetes gave a closely similar insulin response to carbohydrate stimulation, and this suggests that the occurrence of overt diabetes is governed by several factors.

SMOKING

In studies by Friberg *et al*[79] and Fischer[73] smoking habits proved to be more similar in MZ than DZ pairs These results were supported by studies of the Swedish Twin Register[77] Concordance with respect to smoking and non smoking in men was found in 81 per cent of the MZ

pairs against an expected 56 per cent based on the frequency of smokers. Of the DZ pairs 70 per cent were concordant, against 5 per cent expected.

Smoking thus seems to be governed in some measure by genetic factors, from which it follows that the habit may be regarded as an environmental trait linked to the genetic constitution.

PREREQUISITES FOR THE PRESENT STUDY

The evidence provided by the research to date points to a multifactorial aetiology for CHD. Some of the factors found to be associated with CHD are almost certainly of a causal nature, but so long as there is no convincing proof that a reduction of such a factor is accompanied by a significant lowering of the incidence of CHD we shall not be in a position to infer a definite causal relationship. Nor are we certain of the implications of the different risk factors for different clinical manifestations of CHD.

The role of genetic factors in the occurrence of CHD and its various manifestations also remains to be ascertained.

The results of the few twin studies performed to date have not established the relative significance of heredity and environment. The problem is a complex one: for example, the relative importance of heredity would appear to vary with age and sex, and Danish and Swedish twin studies point to a stronger influence of environment in the case of men, particularly below the age of 60.

One of the objects of the present study was to examine the significance of heredity for the occurrence of CHD and its various clinical manifestations in men of working age, and to ascertain which factors in general might be associated with these manifestations.

Principles for a study of coronary heart disease in twins

The dependence of certain traits on heredity can be analysed by comparing MZ and DZ pairs with respect to the concordance or the intrapair variation of the trait. The importance of environmental factors for a particular trait can be examined with genetic factors under control. The theoretical prerequisites for the assessment of the results provided by a study of twins with clinical CHD—requirements that form the basis for the present study—will be outlined below.

INFLUENCE OF HEREDITY ON CHD

By comparing the concordance with respect to CHD in MZ and DZ pairs in a twin population or a representative selection from such a population an estimate of the extent to which genetic factors are responsible for the disease is obtained. The concordance may then relate to either a well defined manifestation, such as infarction, or less specific manifestations.

A significant difference in concordance rate between MZ and DZ pairs points to the influence of *genetic factors. However, the absence of a significant* difference does not necessarily imply that genetic factors are without importance for a disease with a probably multifactorial aetiology. Another source of error is the limitations inherent in the methods for diagnosing CHD with the consequent risk of registering too few concordant pairs. A concordance analysis may however disclose tendencies in the influence of heredity on CHD.

FACTORS RELATED TO CHD ANALYSED IN DISCORDANT PAIRS

Discordance, too, may relate to a certain well defined manifestation of CHD or to any sign or symptom of CHD. Here, too, clinically demonstrated differences do not necessarily imply pathologic differences. This source of diagnostic error

In this study the concordance rate is taken as the ratio of the number of concordant pairs to the total number of pairs having at least one affected partner: it is expressed as a percentage.

is, however common to all studies where an attempt is made to classify the material according to the presence or absence of demonstrable CHD

Since MZ twins are genetically identical CHD-discordance must be due to environmental factors these may be identified by comparing MZ co-twins with and without CHD for a factor that is of a hereditary nature there will be no intra pair difference. The environmental factors may also be identified in discordant DZ pairs for DZ co-twins share half of the genes.

FACTORS RELATED TO CHD ANALYSED IN GENETICALLY UNRELATED GROUPS

A twin material can be examined in the same way as in conventional population studies by selecting only one partner of each pair[47] these will then constitute a series of unrelated subjects, and the results obtained may be compared with those yielded by a study of pairs. If it is desired to compare, with respect to certain factors, groups with and without manifestations of CHD concordant pairs may be used. Pairs concordant as regards the presence of CHD are then compared, as a group with pairs concordant with respect to the absence of CHD Any differences between these 2 types of concordant pairs in respect of a certain factor reflect, though not quantitatively the differences that may be expected in the same group comparison of the presence and absence of CHD in a conventional population study The results can be compared with those obtained in a study of discordant pairs.

Purpose of the present study

The object of the present study was accordingly (*i*) to examine the concordance rate for various manifestations of CHD in MZ and DZ pairs selected from a population of male twins of working age, and (*ii*) to study in discordant pairs *intrinsic* factors associated with CHD including anthropometric factors, blood pressure, lipids and uric acid in serum and diabetes mellitus, and *extrinsic* factors such as smoking, physical activity and psychosocial variables

General procedures

COLLECTION OF TWINS WITH SYMPTOMS OF CORONARY HEART DISEASE

The material for the investigation was obtained from the Swedish Twin Register From this a basic material was selected comprising males aged 42 to 67 years. By a two-stage screening procedure consisting of a postal questionnaire and a preliminary interview the final material was obtained this included twins with CHD manifested as angina pectoris or symptomatic infarction (Table 1)

The Twin Register

The Swedish Twin Register compiled at the Department of Environmental Hygiene, Karolinska Institute and the National Institute of Public Health was intended primarily for examining the effect of certain environmental factors, including smoking, on the occurrence of chronic diseases of the respiratory tract and circulatory organs. From questions relating to similarity as children some 3600 of the 11 000 pairs were tentatively judged to be monozygotic. In 1967 a new questionnaire was sent to the twin pairs both members of which were alive, requesting information on symptoms of coronary disease, smoking habits and other environmental conditions. It is from this questionnaire study that the material for the present investigation was obtained.

TABLE 1 Collection of twins with CHD symptoms

	No. of pairs MZ	DZ[a]	Designation
Male pairs in Twin Register 1967 born 1900–25			
MZ	1262		
DZ[a] in 10 län		904	
Completing questionnaire	1860[b]	1350[b]	Basic material
Infarction, angina pectoris			
Questionnaire	92	78	Crude selection
Preliminary investigation	54	50	Refined selection
Complete pairs for CHD diagnosis	51	40	Final material

[a]Including pairs of unknown zygosity in the Twin Register
[b]Number of individual

The basic material

As the present study was restricted to male pairs of working age only those born from 1900 to 1925 were included in the basic material. The tentatively monozygotic pairs (MZ) numbered 1262, of which 1860 individuals replied to the questionnaire. The selection of tentatively dizygotic (DZ) pairs and pairs of undetermined zygosity (XZ) was restricted not only to the same age range as the MZ pairs but also to those living within a geographically smaller area—"10 län" (Fig. 2) The DZ and MZ pairs numbered 904, of which 1350 individuals completed the questionnaire. "10 län" consisted of 10 counties of central Sweden, with a population distribution and socio-economic structure that may be regarded as comparable with that of the country as a whole. It includes the largest of Sweden's 3 metropolises (Stockholm) agricultural and forestry areas and moor and highlands.

COMMENTS

As pointed out earlier, the object of the study was to compare the MZ and DZ pairs for concordance with respect to clinical CHD and to examine the discordant pairs regarding factors that

are considered to be associated with CHD The selection of DZ pairs from the Twin Register to get approximately the same number of DZ as MZ pairs was made on a geographic basis and would be unlikely to affect the prevalence of CHD differently in the MZ and DZ pairs. The concordance would then probably also be unaffected. Since the genetic factor is completely under control only in the MZ pairs, an attempt was made in the first place to obtain as many such discordant pairs as possible for examination of the factors associated with CHD

Crude selection procedure

In the collection of a material that should include twins with CHD it was considered justified to select subjects with symptomatic infarction or angina pectoris according to the results of the 1967 questionnaire investigation.

SYMPTOMS OF CHD ACCORDING TO THE QUESTIONNAIRE

History of infarction.—In the questionnaire one of the questions on the state of health requested information on any prior myocardial infarction, including the date and any admission to hospital. The reliability of a patient's statements on prior infarction is dependent on the information he received concerning his illness and on his own interpretation of the term infarction. In the questionnaire this was clarified by giving an alternative layman's term. It was obvious from the outset that the patient's statements required checking by personal interview possibly combined with an inspection of hospital and other records.

Angina pectoris—Rose[103] has derived a method for standardized identification of persons with symptomatic CHD by the use of questionnaires in epidemiologic investigations on the occurrence of ischaemic heart disease. Part of the questionnaire relating to angina pectoris is based on the most typical symptom, angina on effort. With this standardized procedure for recording the history it has been found possible in personal interviews to select persons with CHD confirmed by ECG and also in some measure to predict subsequent infarction[104] The questions that provided the basis for diagnosing angina pectoris in this manner were used, in a Swedish translation, for the mailed questionnaire of the 1967 twin investigation. The questions had the following purport

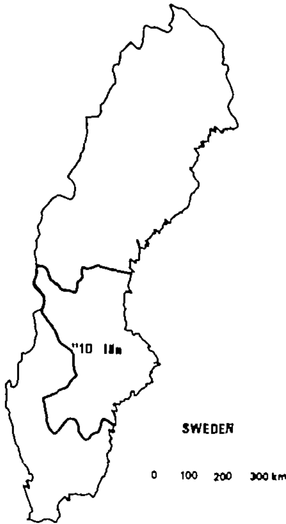


Figure 2 Geographic area 10 län boundary for selection of DZ pairs

(1) Have you ever had pain or discomfort in the chest?
(2) If so when?
   ( ) When agitated or excited
   (b) When in a hurry or walking uphill
   (c) When walking at normal pace on level ground
   (d) Under other circumstances

(3) What do you do if you get such pain or discomfort when out walking?
   (a) Stop or walk more slowly
   (b) Take medicine and go on at the same speed
   (c) Continue at the same speed without taking medicine
(4) If you stop whether or not you have taken medicine, what happens to the pain or discomfort?
   (a) It usually passes within 10 minutes
   (b) It usually remains for more than 10 minutes
(5) Where is the pain or discomfort located?
   (a) In the middle of the chest
   (b) In the left area of the chest
   (c) In the left arm
   (d) Elsewhere

Angina pectoris was regarded tentatively as being present if the answer to question 1 was 'Yes' and if the pain was stated to appear during walking, and disappeared within 10 minutes on slowing down or stopping or taking medicine and was located in the middle or left of the chest.

CRUDE SELECTION

The crude selection consisted of the twins from the basic material who according to the questionnaire were considered to have infarction or angina pectoris, as symptoms of CHD. They numbered 189 in 170 pairs thus, in 19 pairs both partners reported having had symptoms of CHD. Thirty-two of the 189 stated that they had had infarction and 155 angina pectoris and possibly also infarction. Two subjects did not give clear replies to the questions but mentioned "coronary vascular spasm".

COMMENTS

A mailed questionnaire for epidemiologic examination of the prevalence of angina pectoris has also been used by Reid[159] in a study of migrants.

The validity of the diagnosis angina pectoris according to the questionnaire compiled by Rose[162] and used in personal interviews was satisfactory for epidemiologic purposes. The reliability of a questionnaire diagnosis of angina pectoris as a symptom of CHD has been reported by Cederlöf, Jonsson & Lundman[49] in 1966. 216 men aged at least 38 years were submitted to an examination for clinical evidence of CHD, namely the presence of angina pectoris according to the WHO Technical Report Series[203] and ECG changes indicative of coronary insufficiency recorded in connection with exercise or pathologic resting ECG showing signs of past myocardial infarction. Of these 216 men 8 had angina pectoris according to their answer to the questionnaire. 4 of these recorded no clinical signs of CHD, and 2 of the remaining 208 had clinical coronary insufficiency. The questionnaire thus detected 4 out of 6 patients with clinical symptoms, while 4 were false positives.

A corresponding examination of the reliability of the postal questionnaire in the diagnosis of clinical CHD has been made by Glasunov[89]. Out of 548 male clerical workers sent the questionnaire 420 answered and 317 were examined for the occurrence of effort angina in accordance with Rose's criteria accepted by WHO. Of 15 persons thus recorded as having angina pectoris 6 (40 per cent) were judged at the personal interview to have effort angina; the corresponding figure for the 302 persons without angina pectoris according to the questionnaire was 10 (3 per cent). Although the diagnosis of angina pectoris by this technique would seem to have been less reliable than when the questionnaire was used in a personal interview, the percentage of suspected cases detected by the postal questionnaire was high, to judge from the relatively small number of confirmed angina pectoris cases found in the groups that, according to the questionnaire, did not have this symptom. It would therefore seem reasonable to use the questionnaire for screening, and to supplement it with a more specific method for the diagnosis of angina pectoris.

Refined selection procedure

PRELIMINARY INTERVIEW

As pointed out above, it was considered necessary to make a closer examination of the information relating to a history of infarction. There

TABLE 2 Distrib tion of crud and refined elections with respect to age and tentati zygosity

	No. of pairs	Age						Tentativ zygosity					
		42—50		51—60		61—67		MZ		DZ		XZ	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Crude selection	170	35	20	81	48	54	32	92	54	69	41	9	5
Excluded	66	19	29	33	50	14	21	38	58	25	38	3	4
Refined selection	104	16	15	48	46	40	39	54	52	44	42	6	6

was, moreover reason to expect that angina pec toris would be overdiagnosed on the basis of the questionnaire. To reduce the risk of false positives a preliminary appraisal of the CHD symptoms reported in the questionnaire was made This was usually done on the telephone, but in some cases at a personal interview When a history of infarction had been recorded the available re cords were examined.

Hospitalized patients with a diagnosis of myocardial infarction and those reporting central chest pains of at least 30 minutes duration were accepted tentatively as cases of infarction.

A tentative diagnosis of angina pectoris was made where there had been pains in the chest due to effort and generally passing on resting.

REFINED SELECTION

Three of the 189 twins comprising the crude selection were not accessible for the preliminary assessment. In the other 186—in 167 pairs—the appraisal could be made. Seventy persons had reported symptoms that were not considered indicative of CHD and thus excluded 63 of the 167 pairs from the further study The remaining 116 persons, distributed 104 pairs that con stituted the refined selection, were invited to attend for a clinical examination, the object of which was stated to be a general medical check

The pairs excluded from the crude selection were younger than those n the refined selection—as would be expected (Table 2) it being consistent with the increase in the prevalence of CHD with age. The proportion of pairs tentatively classed as monozygotic did not differ appreciably the 2 groups—58 and 52 per cent for the excluded pairs and the refined selection, respec tively The modification of the material after the ref ned selection thus amounts to a rise in age, while the proportion of MZ to DZ pairs remained essentially the same

COMMENTS

At the preliminary interview and the inspec tion of the available records t was evident that some of the subjects reporting prior infarction had misconstrued the diagnosis. In other cases the records were either not availabl or they did not exclude the possibility of infarction. The preliminary interview relating to reported angina pec toris did not always disclose the various items in the history that are necessary to confirm diag nosis of angina pectoris. So as not to risk loss to the study of subjects with CHD at the refined selection a certain over-diagnosis of both angina pectoris and nfarction was considered to be justified.

Final material

Of the 104 pairs of the refined selection invited to attend the examination 13 were discarded because one twin could not be examined. In 6 of these 13 pairs the twin with symptoms of CHD refused examination and in 4 other pairs the co-twin refused. In 2 pairs it was impossible to communicate with the co-twin and in the remaining pair he was admitted to hospital after an accident.

The *final material* thus comprised 91 pairs where both members accepted to be examined. The distribution of these and the discarded 13 pairs with respect to zygosity and age is shown in table 3

TABLE 3 Distribution of final material and discards at examination with respect to age and zygosity

	Final material			Discards		
	MZ	DZ	Total	MZ	DZ	Total
Age 61—67	20	13	33	2	5	7
51—60	24	20	44	2	2	4
42—50	7	7	14	1	1	2
Total	51	40	91	5	8	13
Mean	57.8	56.8	57.4	57.6	58.6	58.2

COMMENTS

The purpose of the screening procedure by which the final material for this investigation was compiled was to select pairs in which at least one twin had CHD manifested as infarction or angina pectoris. This procedure included a crude method—the questionnaire which yielded a material from which 104 pairs were selected by a refined method—the preliminary interview

Thirteen pairs were discarded in the examination of the refined selection. Since each pair constitutes a unit for the examination the risk of loss to a twin study is greater than in the case r a series of individuals. In spite of repeated itions to participate in the examination and to perform the examination at home the ion of pairs where the information on p ce of clinical CHD could be obtained in twins remained at 87 5 per cent. The loss 3 pairs did not change the age distribution ween MZ and DZ pairs in the final material m those distributions obtained for the refined ection. How these pairs might have affected e results will be discussed in the appropriate ctions.

As the screening procedure probably introduced biases, the magnitude of which it is difficult to assess, the final material cannot be taken as a basis for determining the prevalence of CHD in the twin population. There is however no reason to belie that these biases affected the MZ and DZ pairs differently and the comparisons between these zygosity groups would therefore seem to be valid.

The representativeness of the twins comprising the Swedish Twin Register has been investigated by Cederlöf[47] with respect to age and a number of sociological variables. As regards age, the twins were not representative, probably owing in part to the fact that the Register originally contained only pairs both members of which were living With regard to medical variables the twins differed from the total population in that the prevalence rate of the questionnaire diagnosis angina pectoris was lower and the symptom cough was higher in the twins than in the control group There were also small differences between the twins and the total population in respect of some sociological variables.

As the final material of twins for the present investigation thus cannot be representative of the Swedish population as a whole, no valid quantitative comparison can be made between the twin material and the total population in respect of the variables studied It is, however permissible to compare a correlation obtained within the twin material with the corresponding correlation obtained within some other populations

INDEX SUBJECTS

The twins judged in the refined selection to have symptoms of CHD were designated index subjects In 12 pairs both twins were tentatively classed as having symptoms of CHD and here one was drawn at random as the index subject. All 12 pairs were included in the final material, in which 91 index subjects could thus be compared with their respective partners* as regards clinical manifestations of CHD

FINAL DIAGNOSIS OF CHD

Time place and extent of the examination

The clinical examinations were conducted between February 1967 and August, 1968. During this period one twin in 6 pairs died before the intended examination could be carried out. In 4

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* The term partner in the following will be reserved for the co-twin of an index subject.

TABLE 4 Basis for diagnosis of CHD

		PARTNERS			
		S	H	R	N
	S	75	1	—	76
INDEX	H	3	6	—	9
SUBJECTS	R	2	2	2	6
	N	80	9	2	91

S Examined at the Serafimer Hospital
H " " home
R Diagnosis through hospital records

of these the diagnosis of CHD was confirmed at autopsy and in one case by the hospital records. For the sixth subject the diagnosis was based on the results of the postmortem examination conducted to confirm the cause of death. The brothers of 2 of the deceased were not examined because a diagnosis of infarction was obtained from the hospital records

Altogether 174 persons were examined, 156 of them at the Serafimer Hospital and 18 at home. The 75 pairs where both twins were examined at the Serafimer Hospital will be referred to as group I, and the other 16 as group II (Table 4)

The examinations comprised a history a physical examination, ECG, usually also during exercise, and an interview on psychosocial conditions

At the Serafimer Hospital 2 persons a day were examined. The examination was introduced at 8 a.m with blood and urine analyses and also included X rays of the heart and lungs and an interview on dietary habits.

When the subject was prevented from attending the Serafimer Hospital the examination was performed *at home* As it was carried out at different times of the day no analysis of blood specimens was included.

Period covered by the examination of the co-twins

In the majority of cases the index subjects were examined before or at same time as their partners. The distribution of the time elapsing between the examination of the index subjects and their partners for the MZ and DZ pairs is shown in table 5 For the pairs where one twin died the period was counted from the date of decease until the examination of his brother

Of the 2 MZ partners examined after more than 6 months, one who was examined 11 months after his brother s death, had had symptoms resembling angina pectoris for about one year For the other partner, who was examined after 7 months, there were only ECG changes

Of the 2 DZ partners examined after more than 6 months one, who was examined 19 months after his brother reported no symptoms of CHD The other, examined 10 months after his brother s death, also showed no evidence of CHD

As most of the other partners, of both MZ or DZ pairs, had been examined at about the same time as the index subjects, it is unlikely that the interval between the examinations affected the diagnoses of CHD differently for the MZ and DZ partners.

TABLE 5 Interval between examinations of index subjects and their partners

	MZ	DZ
Partner examined		
Before or at same time as index subjects	31	22
Within 1 week	5	4
1 month	7	7
6 months	5	4
After 6 months	2	2
Through records	1	1
Total pairs	51	40

ZYGOSITY DETERMINATION

For about 95 per cent of the pairs in the Twin Register a tentative determination of zygosity was made on the basis of the replies to questions relating to resemblance— alike as two peas in a pod when children If both partners gave consistent answers on similarity or dissimilarity the pair was classified as monozygotic or dizygotic, respectively The validity of this method has been

examined by Harvald & Hauge[39] and by Cederlöf *et al.*[46] Cederlöf found that for all but one of the 72 pairs classed as monozygotes by this method a serologic zygosity determination was confirmatory.

The classification of the 91 twin pairs comprising the final material in this study was checked in the investigation by repeating the questions relating to similarity and by comparing photographs of the twins taken in connection with the investigation. In the case of the slightest doubt as to zygosity a serologic determination was performed as in the case of the unclassified pairs. It was carried out at the National Laboratory of Forensic Medicine and comprised the blood group systems ABO, MN, P, K, KE, FY, Jk and Rh and the serum groups Gm, Gc and Hp. The classification of the monozygotic pairs may thus be regarded as being adequately confirmed. As regards the dizygotes the confirmation is not so firm since it was based essentially on an estimate of dissimilarity and it is a familiar fact that even monozygotic twins may display differences in appearance.

COMMENTS

The smaller a twin material is the more important is the zygosity classification if the results of comparisons between monozygotes and dizygotes are to be meaningful. Certainty as to zygosity can only be obtained in pairs where a common chorion membrane has been found which rules out the possibility of dizygosity. A pair with a divided chorion can, however, also be monozygotic[10]. Of the other methods for determining zygosity the serologic blood group determination is at present the most reliable. The suitability of this method, however, is dependent on the number of serologic groups compared, for the use of this test on a large number of pairs would be quite expensive.

STATISTICAL METHODS

The intra-pair comparisons of the qualitative variables such as symptoms, diagnoses and ECG findings are reported in contingency tables, in which the index subjects form the rows and the partners the columns. The number of pairs is denoted by N_p and the number of subjects by N_s. [illegible]rdance rate for a certain trait is given as [illegible] ratio of the number of concordant pairs to the total number of pairs having at least one twin displaying the trait.

Differences between the proportions were examined by the chi-square test. Yates's correction for discontinuity was applied (χ^2_c). If the direction of the distribution could be expected the one-tailed probability was calculated.

The differences between means and the mean intra-pair differences were examined by Student's *t* test.

The null hypothesis of no difference was rejected at the significance levels of 5 per cent ($P<0.05$*), 1 per cent ($P<0.01$**) and 0.1 per cent ($P<0.001$***).

The statistical methods used for calculating intra-pair differences of quantitative (*Section IV*) and qualitative (*Section V*) variables are described in the appropriate sections.

Intra-pair occurrence of coronary heart disease

RECOGNITION OF CORONARY HEART DISEASE

Symptoms of myocardial infarction and angina pectoris

The first part of the clinical examination comprised the case history and physical examination. The results of the history were supplemented with information from any hospital files relating to visits to a doctor or admission of the patient to the hospital they were scrutinized chiefly for the presence of myocardial infarction.

MYOCARDIAL INFARCTION

Verified infarction

The diagnosis of infarction was considered established if one of the following criteria was fulfilled

1 Diagnosis at autopsy
2. Central chest pains for at least 30 minutes, combined with

(*a*) pathologic ECG with localized elevation of S-T segment on admission, development of isolated negative T waves or presence of abnormal Q waves, (Q 1—2 according to the Minnesota Code*) *or*

(*b*) laboratory signs of myocardial damage (rise in S-GOT above 50 I U) during hospitalization

Suspected infarction

Central chest pains lasting for at least 30 minutes unaccompanied by the above signs of myocardial infarction were regarded as possibly indicative of infarction

ANGINA PECTORIS

For the history the schedule worked out by Rose at the London School of Hygiene and Tropical Medicine[147] was used

Angina pectoris was defined as pains in the sternal area—whether or not they radiated to the arms or towards the jaws—*or* pains to the left of the anterior chest radiating to the left arm, that accompanied physical effort and disappeared or were alleviated, within 10 minutes of resting or taking a nitroglycerine preparation.

Suspected angina pectoris was diagnosed when some but not all of the above criteria for angina pectoris were fulfilled, and also when, from the patient's description of the pain, there was some doubt whether the condition was actually angina pectoris.

DURATION OF SYMPTOMS

The duration of the above symptoms of CHD was reckoned from the date of their onset until the examination, and was expressed in years.

Physical and radiologic examination

For twins examined at the Serafimer Hospital the physical examination was supplemented by a radiologic examination of heart and lungs. Exposures were taken in 2 planes with the subject standing, and determinations of the total and relative heart volumes[108] were performed by an experienced radiologist.

Other symptoms or signs

The examination also covered other symptoms and signs such as cardiac arrhytmia, peripheral circulatory disturbances, and respiratory gastrointestinal and motor symptoms.

ECG examination

The clinical examination comprised ECG registrations at rest and in most cases during exercise The intra pair distribution of the ECG examination of both types is shown in table (

* See Appendix

TABLE 6. Resting and exercise ECG: index subjects versus partners. MZ and DZ pairs

		RESTING ECG					
		MZ PARTNERS			DZ PARTNERS		
		Performed	Not performed	N	Performed	Not performed	N
INDEX SUBJECTS	Performed	47	—	47	38	—	38
	Not performed	4*	—	4	1	1	2
	N	51	—	51	39	1	40

		EXERCISE ECG							
		MZ PARTNERS				DZ PARTNERS			
		S	H	Not performed	N	S	H	Not performed	N
INDEX SUBJECTS	S	41	—	—	41	33	1	—	34
	H	—	1	1	2	1	—	—	1
	Not performed		3	3	8	3	1	1	5
	N	43	4	4	51	37		1	40

* ECG for one partner obtained from record
S Examined at the Serafimer Hospital
H " home

PROCEDURE

A resting ECG in the supine position was obtained for all 174 subjects examined. At the Serafimer Hospital a four-channel electrocardiograph was used, and for the examination at home a corresponding three-channel apparatus. Six extremity leads (I—III, aVR, aVL, aVF) and 5 chest leads ($CR_{1, 2, 4, 5, 7}$) were used.

In the *examination at the Serafimer Hospital* an ECG during exercise was recorded in all 156 cases except one with confirmed acute infarction. The work was performed on a mechanically braked bicycle ergometer[2] as described by Sjöstrand[174]. The initial load was 150—300 kgf m/min depending on the physical condition of the subject. After each 6-minute period the load was raised by the initial amount, and the test was discontinued when symptoms of angina pectoris were noticed or when the subject was obliged to stop because of fatigue. The highest load was 1500 kgf m/min. In a few cases it was necessary to discontinue the test earlier because of joint disorders and in one case because of a distinctly pathologic ECG reaction unaccompanied by the above subjective symptoms. The ECG recording was performed with the leads $CH_{2, 4, 5, 7}$ before, every second minute during, and immediately after exercise[4]. Three to 10 minutes after stopping pedalling the ECG was again recorded as for the resting ECG.

For the *examination at home* only the subjects with no confirmed myocardial infarction were submitted to the exercise test. The partners of 2 MZ index subjects who had had infarction could not be tested: one of them had been admitted to hospital for a severe leg fracture and the other had persistent paralysis following a cerebral accident. A similar mechanically braked bicycle ergometer[2] was used, though this did not afford the possibility of an exact grading of the load. For the 9 twins examined at home the test was dis-

Mingograph 42, Elema Schönander AB, Stockholm
Monark Crescent AB, Stockholm
Equivalent to kilopondmeter/min (kpm/min)
In the CH chest leads the indifferent electrode is placed on the forehead to reduce interference from muscle action potentials during the test.

continued either in the case of subjective symptoms owing to the limited facilities for dealing with emergencies outside the hospital. The registration of the ECG during exercise was performed with 3 chest leads (4, 5 and 7) but otherwise the procedure was the same as at the Serafimer Hospital. In no case did complications arise during the exercise test.

INTERPRETATION OF THE ECG

To enable an intra pair comparison of the ECG reaction during exercise to be made, the ECG was interpreted at the *highest comparable heart rate* (HCHR)—defined as the highest heart rate recorded by the twin with the lower physical performance. The load at this rate was termed the *highest comparable load* (HCL). The ECG was also interpreted at the *highest heart rate* (HHR). The load at this level was designated the *highest load* (HL).

The ECG findings were codified in accordance with a system devised by Astrand *et al* [12] which is a modification of the Minnesota Code[13].

From the *resting ECG* the following findings are reported: arrhythmias, abnormal Q waves, intraventricular conductive defects (IVCD), abnormal S-T changes and T waves and signs of left ventricular hypertrophy (LVH). From the *ECG during exercise* the items reported were arrhythmias, appearance of intraventricular conductive defects and S-T or T wave changes that occurred at HCHR, at HHR and 3—10 minutes after exercise. In cases where the registration at HHR was not interpretable the ECG findings refer to those recorded immediately after exercise.

Definition and grouping of various CHD manifestations

To enable intra pair comparisons of various clinical manifestations of CHD to be made, these were grouped on the basis of the results of the clinical examination and information available from records. The following classification was used.

Group 1 Myocardial infarction.

Group 2 Angina pectoris and one or more of the following ECG findings
At rest—Q 2.
During exercise—Depressed S-T segment (S-T 1-4) in subjects not on digitalis.

Group 3 (*a*) Angina pectoris and any ECG findings not assigned to group 2, *or*
(*b*) ECG findings in accordance with group 2, *or*
(*c*) Suspected infarction or angina pectoris combined with other CHD manifestations.

Group 4 Any of the following findings
(*a*) Suspected angina pectoris without the above ECG changes.
(*b*) ECG findings
At rest—Q 3, depressed S-T segment (S-T 1-3), left-sided or anterolateral bundle branch block.
During exercise—Depressed S-T segment (S-T 1-4) in patients treated with digitalis or appearing at least 3 minutes after exercise.
(*c*) Subjects displaying signs of another heart condition that precluded the possibility of a reliable CHD diagnosis according to any of the above groups.

Group 5 None of the findings mentioned in groups 1—4.

COMMENTS

The grouping of the various manifestations of CHD is largely consistent with the clinically accepted terms myocardial infarction (group 1), coronary insufficiency with or without angina pec

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See *Appendix*

Comprising 2 index subjects with atrial fibrillation prompting treatment and unaccompanied by signs of valvular heart disease, and one with myocardial fibrosis at autopsy.

toris (groups 2 and 3) and suspected CHD (group 4) As pointed out in *Section II* the diagnosis of angina pectoris made on the basis of the replies to the questionnaire is insufficient a penetration of the history is often required in order to clarify the components of the syndrome only then can the symptoms have any clinical implications. For angina pectoris to be regarded as a reliable manifestation of coronary insufficiency in an epidemiologic study strict requirements as to occurrence and site shall, however, be observed—as indicated by Rose[162]

As regards ECG findings as a manifestation of CHD abnormal Q waves, Q 1 are practically pathognomic for prior infarction Q 2, 3 are most probably representative of ischaemic myocardial damage, particularly in examinations of selected materials. This was pointed out by Blackburn and co-workers in connection with the publication of the Minnesota Code[22] By comparing a healthy population and an infarction material with respect to the Q items they found that the widened Q wave criterion—Q 1 3—for a healthy population resulted in an overdiagnosis of about 13 per cent, while the stricter Q wave criterion—Q 1—for the sick group incurred a risk of missing about one third of the cases— diagnostic electrocardiographic criteria are more discriminative in populations in which there is a greater prevalence of heart disease"

In a comparison of clinical findings for an autopsy series comprising 1400 persons in Malmö with the autopsy results in respect of coronary disease Bjurulf Garlind & Sternby[31] found that the specificity of the ECG registration of for example, Q 1 2 was high and that the agreement between this form of clinical CHD sign and changes detected post mortem was of the same order (63 per cent) as for the findings in the history The addition of such ECG items as bundle branch block and arrhythmias diminished the specificity but increased the diagnostic sensitivity

Segmental S-T depression, especially that occurring during exercise[1 33] has proved in several studies to be closely correlated to angina pectoris, and in some measure also to angiographic appearances associated with changes in the coronary vessels[9 44 85 67 113 128] Prospective studies have also shown that patients displaying such changes run a considerably greater risk of myocardial infarction than those without demonstrable S-T depressions[13 17 161] The clinical findings comprised by group 4 are not definitely indicative of CHD as in the case of groups 1 3 In the absence of all these findings CHD may be considered to be unlikely (group 5)

RESULTS

Symptoms of coronary heart disease

Of the 51 index subjects in the MZ group 38 had suffered from myocardial infarction, or had angina pectoris or suspected such symptoms (Table 7) Of the 14 index subjects that had had infarction 3 had died the diagnosis was confirmed at autopsy Of the 10 index subjects with suspected angina pectoris one had died and autopsy disclosed myocardial fibrosis.

Of the MZ partners 12 recorded infarction, angina pectoris or suspected such symptoms Of the 9 partners with either infarction or angina pectoris the index subjects of 7 had similar symptoms. In only one pair had both twins had infarction. One of the 3 MZ partners that had suspected angina pectoris was of a pair whose index subject had died of infarction.

The 40 DZ pairs included 27 index subjects with infarction, angina pectoris or suspected such symptoms in 11 of them the diagnosis of infarction was verified. One of these had died and the diagnosis had been made earlier at the hospital.

Of the 2 DZ partners that had had infarction one had died. Both twins of 3 DZ pairs had infarction or angina pectoris. Both twins of one of these pairs had had infarction.

TABLE 7 Type of symptoms of CHD index subjects versus partners MZ and DZ pairs

		MZ PARTNERS				
		Infarction	Angina pectoris	Suspected angina	No such symptoms	N
INDEX SUBJECTS	Infarction	1	1	1	11	14
	Angina pectoris	2	3	—	8[b]	13
	Suspected angina	1	—	1	9[a]	11
	No such symptoms	—	1	1	11	13
	N	4	5	3	39	51
		DZ PARTNERS				
INDEX SUBJECTS	Infarction	1	1	1	8	11
	Angina pectoris	1	—	—	9[a]	10
	Suspected angina	—	—	—	6	6
	No such symptoms	—	1	4	8	13
	N	2	2	5	31	40

[a]With or without angina pectoris
[b]Including 2 index subjects with suspected infarction
[c]Including 1 subject

Comments

The proportion of infarctions in the index subjects was the same for the MZ and DZ groups (27 5 per cent) as was the percentage of index subjects with angina pectoris (25 per cent) Concordance of verified infarction was found in only one MZ and one DZ pair Concordance with respect to infarction or angina pectoris, however, was found in 7 out of 29 MZ pairs (24 per cent) against 3 of the corresponding 22 DZ pairs (14 per cent) The difference is not statistically significant, but it cannot be ruled out that genetic factors are of significance for the occurrence of the symptoms of CHD mentioned.

DURATION OF SYMPTOMS AND AGE AT FIRST INFARCTION

The duration of the symptoms of definite or suspected CHD for index subjects and partners is shown in table 8. The mean duration for the MZ index subjects was 5 9 years and for the partners 7 6 years. For the DZ index subjects the mean duration was 6 4 years and for the co-twins 5 6 years.

The differences in the duration of CHD symptoms were not significant for either the MZ/DZ or for the index subject/partner comparisons.

The mean age at the first diagnosed infarction was the same for the MZ and DZ twins (Table 9) One MZ twin had had infarction at the age of 28 while his brother did not suffer from angina pectoris until after 40

Other cardiac symptoms

In 13 MZ and 13 DZ index subjects the tentatively recorded symptoms were judged not to be due to infarction or to be of the nature of angina pectoris.

Cardiac symptoms of a different kind occurred in 4 of these MZ and 3 DZ index subjects (Table 10) Two of the index subjects displayed physical and radiographic signs of valvular heart disease (VHD) The symptoms that these reported were of the nature of cardiac insufficiency with dyspnoea on effort. The same applies to an MZ index subject with hypertension. He had an enlarged heart and had previously been treated for hyperthyroidism. The partner also had

TABLE 8 D ation of CHD symptom (5 or) index bject ersus partners MZ and DZ pair

		MZ PARTNERS				
		Duration				
		< 5	5—9	≥ 10	No symptoms	N
	< 5	2	—	3	14	19
	5—9	—	—	1	7	8
INDEX	≥ 10		1	—	6	9
SUBJECTS	No known	1	—	—	1	2
	No symptoms	1	—	1	11	13
	N	6	1	5	39	51
		DZ PARTNERS				
	< 5	1	1	—	7	9
	5—9	1	1	—	8	10
INDEX	≥ 10	—	—	—	6	6
SUBJECTS	No known	—	—	—		2
	No symptoms	2	1	2	8	13
	N	4	3	2	31	40

elevated blood pressure but the heart was of normal size. Three of the index subjects had had symptoms of arrhythmia. One of these a DZ index subject, had had suspected syncope a year before the examination. In the subsequent ECG registration frequent ventricular extra systoles had been registered

In the case of another MZ pair the partner had recorded physical evidence of aortic valvular heart disease. Episodes of arrhytmia had been experienced over the previous 10 years and digitalis had been taken. The index subject of this pair had previously had an ulcer and displayed gastritis-like symptoms but did not fulfil any criteria for symptoms of CHD

TABLE 9 Age at infarction (first diagnosed)

		MZ twins	DZ twins
Age			
Over 60		3	2
51—60		9[a]	6
41—50		5	5
Under 41		1	—
	Total	18	13
	Mean	53 4	53 8

[a] Including the co-twins of one infarction-concordant pair

Comments

As pointed out earlier for angina pectoris to be regarded as reliable evidence of clinical coronary insufficiency a history of the qualities of the symptom was required. Valvular or hypertensive heart disease can produce symptoms reminiscent of coronary insufficiency chiefly dyspnoea. Stenocardiac symptoms in aortic stenosis however preclude a differential diagnosis in respect of angina pectoris due to coronary disease the subject judged to have aortic valvular heart disease had angina like symptoms Occasional arrhythmia unaccompanied by chest pains was not accepted as a symptom of CHD In combination with syncope in one DZ subject, however arrhythmia was considered to justify suspicion of CHD

Other symptoms

Nine MZ and 10 DZ index subjects displayed symptoms that could not be definitely classed as

TABLE 10. Other cardiac symptoms

		Predominating symptoms	Relative heart size*	Clinical findings	Diagnosis at examination
MZ	Index subject	Dyspnoea on effort	560	Systolic murmur apex region	Mitral insufficiency
	Partner		500		Mitral insufficiency
MZ	Partner	*Suspected angina pectoris and arrhythmia*	520	Systolic murmur aorta region	Aortic stenosis
DZ	Index subject	Dyspnoea on effort	680	Systolic murmur *apex region* BP 180/100	Mitral insufficiency? + *hypertension*
MZ	Index subject	Dyspnoea on effort	430	BP 170/105	Hypertension previously hyperthyroidism
DZ	Index subject	Dyspnoea on effort	570	BP 200/95	Hypertension
	Partner	Suspected angina pectoris	460	BP 165/105	
MZ	Index subject	Arrhythmia	400	ECG A-V dissociation	Paroxysmal atrial tachyarrhythmia
MZ	Index subject	Arrhythmia	420	ECG occasional VPB during exercise	Paroxysmal ventricular tachyarrhythmia?
DZ	Index subject	Arrhythmia and syncope	380	ECG VPB at rest	Paroxysmal ventricular tachyarrhythmia with syncope

*Relative heart size in millilitres per square metre of body surface area

being of a cardiac type. One of the 9 MZ and 2 of the 10 DZ index subjects, however showed ECG changes that gave rise to suspicion of coronary insufficiency. In a total of 16 index subjects CHD could thus not be established with the criteria applied here. Seven seemed to have symptoms of a gastrogenic type or biliary symptoms, 3 pain probably *deriving from the cervical or thoracic* spine, and 5 mainly respiratory symptoms. One other index subject had on several occasions been admitted to hospital for diabetes mellitus oligophrenia was also found. He denied having chest pains that he had reported at the preliminary interview.

In one of the 9 MZ pairs the index subjects of which had no cardiac symptoms the partner however had angina pectoris. The index subject of this pair had reported infarction, but this diagnosis could not be verified. The symptoms were judged to be respiratory in type.

In 2 DZ pairs where the index subjects had no definite cardiac symptoms the partners had symptoms reminiscent of angina pectoris. The index subject of one of these pairs had diabetes mellitus and was the above mentioned oligophrenic. The index subject of the other DZ pair where the partner was suspected of having angina pectoris probably had symptoms of biliary dyskinesia.

Comments

The organic symptoms that probably led to a false diagnosis of angina pectoris in 16 of the index subjects are representative of some of the known differential diagnoses in coronary disease. It must, however be stressed *that these* are only alternative explanations of previously reported

TABLE 11 Q waves: index subjects versus partners. MZ and DZ pairs

	Q	MZ PARTNERS 1	2	3	Normal	Not rec	N	DZ PARTNERS 1	2	3	Normal	Not rec	N
	1	—	-	—	3	—	3	—	—	—	1	—	1
	2	—	—	—	3	—	3	—	—	—	2	—	2
INDEX	3	—	—	1	1	—	2	—	—	—	3	—	3
SUBJECTS	Normal	3	—	1	35	—	39	1	—	2	29	—	32
	Not rec	1	—	—	3	—	4	—	—	—	1	1	2
	N	4	—	2	45	—	51	1	—	2	36	1	40

symptoms reminiscent of infarction or angina pectoris and were not always thoroughly examined. CHD cannot, of course, be completely ruled out in these 16 cases but they did not meet the criteria for CHD groups 1-4.

ECG findings

RESTING

Q, S-T and T items.—The number of abnormal Q waves distributed by Q 1–3 is shown in table 11. Eight MZ index subjects and 6 partners registered these categories. In one pair both twins had registered items Q 3. In one pair where the partner recorded Q 1 the index subject had died from infarction. Four partners with abnormal Q waves had index subjects with normal Q waves.

Of the DZ index subjects 6 had abnormal Q waves against 3 of the partners. None of the DZ pairs was concordant with respect to abnormal Q waves.

Only a few twins recording S-T 1–3 were found (Table 12). In 2 of the DZ pairs both twins registered S-T 1–3 at rest. In one DZ index subject an elevated S-T was recorded as a sign of acute infarction. The partner in this pair had normal S-T segments.

TABLE 12 S–T segment in resting ECG: index subjects versus partners. MZ and DZ pairs

	S–T	MZ PARTNERS 1–3	4, 5	6–8	Digitalis	Not rec	N
	1–3	—	—	1	—	—	1
	4, 5	—	—	8	1	—	9
INDEX	6–8	1	2	26	1	—	30
SUBJECTS	Digitalis	—	1	5	—	—	6
	Not rec	—	—	3	2	—	5
	N	1	3	43	4	—	51

	S–T	DZ PARTNERS 1–3	4, 5	6–8	Digitalis	Not rec	N
	1–3	2	—	—	1	—	3
	4, 5	—	—	2	—	—	2
INDEX	6–8	—	3	25	1	—	29
SUBJECTS	Digitalis	—	1	1	2	—	4
	Not rec	—	—	2*	—	—	2
	N	2	4	30	4	—	40

* Including one index subject with elevation of S–T segment

TABLE 13 T waves in resting ECG, index subjects versus partners, MZ and DZ pairs

	T	1—3	4	Normal	Digitalis	Not rec	N
		MZ PARTNERS					
	1—3	1	2	4	1	—	8
	4	2	4	6	—	—	12
INDEX	Normal	1	5	13	1	—	20
SUBJECTS	Digitalis	1	2	3	—	—	6
	Not rec	—	1	2	2	—	5
	N	5	14	28	4	—	51
		DZ PARTNERS					
	1—3	2	—	4	2	—	8
	4	1	1	4	—	—	6
INDEX	Normal	2	3	16	—	—	21
SUBJECTS	Digitalis	1	—	1	2	—	4
	Not rec	—	1	—	—	—	1
	N	6	5	25	4	—	40

Iso-electric or diphasic T waves were registered in 8 MZ index subjects not on digitalis treatment (Table 13). Both twins of one pair had the same features. If flat T wave (T 4) is included, such findings were recorded in both twins of 9 MZ pairs. Two DZ pairs were concordant with respect to T 1-3. Items T 1-4 were recorded in both twins of 4 DZ pairs.

Other ECG findings at rest.—The ECG findings in left ventricular hypertrophy (LVH), intraventricular conductive defect (IVCD) and ventricular premature beats (VPB) are shown in table 14. In 2 MZ pairs both twins presented LVH. Both twins of one DZ pair had LVH. No concordance with respect to other ECG findings at rest was observed in MZ or in DZ pairs.

DURING AND AFTER EXERCISE

Heart rates and loads.—In 42 MZ pairs and 35 DZ pairs both twins were submitted to an ECG examination during exercise and ECG comparisons at HCHR were made (Table 15). There was no significant difference in HCL between the partners and index subjects for the MZ or the DZ pairs.

The HHR was greater for both MZ and DZ partners than for the index subjects, as was the final load (HL). However, the differences in HL were not significant for the MZ pairs. It should be observed that several of those twins with a predictably low work capacity—the infarction cases—were not submitted to the exercise test.

S-T items.—At HCHR S-T 1-4 were registered in 14 out of 37 MZ index subjects (38 per cent) not receiving digitalis, and in 11 of the 31 DZ index subjects (36 per cent) (Table 16).

The *maximum change* in the S-T segment registered for index subjects and partners during or after exercise are shown in table 17. The number of subjects with S-T 1-4 increased, owing in particular to changes that appeared after exercise. Nineteen of the 37 MZ index subjects (51 per

TABLE 14 Other findings in resting ECG

		LVH*	Intraventricular conductive defect: LBBB	RBBB	ALBB	VPB
MZ	Index subject	3	—	3 (2)	—	3
	Partner	3	—	2	1	2
DZ	Index subject	4	—	1 (1)	1	2*
	Partner	2	—	1 (1)	—	—

*Ventricular activation time >0.05 and/or high amplitude R waves (> 33 mm in CR_5 or)
( ) Incomplete RBBB
*Including one subject with frequent unifocal VPB

TABLE 15 Highest comparable heart rates (HCHR) and loads (HCL) highest heart rate (HHR) and load (HL)

		N	HCHR (beats/min) Mean	HCHR (beats/min) S D	HCL (kgf m/min) Mean	HCL (kgf m/min) S D	N	HHR (beats/min) Mean	HHR (beats/min) S D	HL (kgf m/min) Mean	HL (kgf m/min) S D
MZ	Index subjects	42	147 5	21.5	833	260[a]	43	150.7	22 0	870	271
	Partners	42	150 7	20.3	827	273[a]	47	162.0	19.7	938	220[a]
DZ	Index subjects	35	143.8	26 6	873	277[a]	35	146 3	26.3	897	262[a]
	Partners	35	144 4	23.6	838	303[a]	39	158 9	22 8	1000	261[b]

[a] Mean based on N —1 subjects because in the examination performed at home no grading of load was made
[b] Likewise for N —2 subjects
[c] Likewise for N —4 subjects

TABLE 16. S–T segment during exercise at HCHR, index subject versus partners MZ and DZ pairs

		MZ PARTNERS						
	S–T:	1—3	4	5	6—8	Digitalis	Not rec	N
INDEX SUBJECTS	1—3	3	—	—	6	2	1	12
	4	—	—	1	1	—	—	2
	5	—	—	—	—	—	—	—
	6—8	3	—	2	18	—	—	23
	Digitalis	2	—	—	2	—	2	6
	Not rec	—	—	—	—	2	6	8
	N	8	—	3	27	4	9	51
		DZ PARTNERS						
INDEX SUBJECTS	1—3	5	—	—	6	—	—	11
	4	—	—	—	—	—	—	—
	5	—	—	—	—	—	1	1
	6—8	1	—	—	18	—	—	19
	Digitalis	1	—	—	1	2	—	4
	Not rec	—	—	—	1		2	3
	N	7	—	—	26	4	3	40

TABLE 17 Maximum S–T changes during or after exercise

	S–T	1—3	4	5	6—8	Dig	Not rec	N
MZ	Index subjects	17 (3)	(1)	3 (3)	15	6	8	51
	Partners	14 (3)	2 (2)	3 (1)	24	4	4	51
DZ	Index subjects	13 (2)	—	1	17	4	5	40
	Partners	11 (4)	1 (1)	1	22	4	1	40

Figures in parentheses relate to cases with maximum S–T change at least 3 min after exercise

TABLE 18 Other ECG changes during exercise

		T wave change[a]	IVCD	VPB[a]
MZ	Index subjects	2	1	4
	Partners	1	—	2
DZ	Index subjects	—	—	1
	Partners	1	1	3

In subjects without digitalis therapy
From negative in rest to positive during exercise

cent) and 16 of 43 partners (37 per cent) registered S-T 1-4. Of the 31 DZ index subjects 13 (42 per cent) had S-T 1-4 as did 12 of the partners (34 per cent)

Other ECG changes.—Other ECG findings recorded in connection with the exercise test are presented in table 18. The changes did not occur in both twins within the pairs in one MZ pair however, where the index subject developed IVCD during exercise the partner had a negative T wave after exercise. In another MZ pair where the partner had previously had infarction an initially negative T wave changed to positive during exercise the index subject of this pair recorded a negative T wave after exercise. All the registered VPB were incidental and unifocal.

COMMENTS

The tendency for greater concordance in MZ pairs than DZ pairs in respect of symptoms of CHD was not reflected in the ECG changes registered at rest or during exercise. Half of the twins with angina pectoris recorded an abnormal Q wave at rest or S-T changes of the ischaemic type (S-T 1-4) during exercise (Table 19). Since several of those with infarction had died, had been examined at home, where the exercise ECG was not performed, or were being treated with digitalis, no comparison could be made with their co-twins in respect of S-T segment or T wave. A comparison of MZ and DZ pairs with regard to the concordance of those isolated ECG changes that are indicative of coronary insufficiency thus affords no basis for assessing the significance of heredity for CHD

Intra-pair comparison of CHD diagnosis

In 49 of the examined 51 MZ and all 40 DZ pairs, respectively both co-twins could be classed in accordance with the above described grouping. The intra pair distribution is shown in table 20. In the case of the partners of 2 MZ pairs whose index subjects had infarction an accurate diagnosis was impossible because the exercise ECG could not be registered. One partner who, just before the examination was to be carried out as agreed, had suffered severe fracture of the legs, had no symptoms of coronary disease and the resting ECG was normal. The other partner, who was suffering from the effects of a cerebral acci-

TABLE 19 Abnormal Q waves or S–T depression in twins performing the exercise test

	N	Q 1, 2 or S–T 1–4 during exercise No.	%	Q 3 or S–T 1–4 after exercise[a] No	%	*Subjects on digitalis* included
CHD symptoms						
Infarction	18	14	78	—	—	2
Angina pectoris[c]	29	16	55	5	17	1
Suspected angina[d]	23	4	17	1	4	1
No such symptoms	94	4	4	14	15	1

[a] In subjects without Q 1, 2 and S–T 1–4 *during* exercise
[b] With or without angina pectoris
[c] Including 2 subjects with suspected infarction
[d] Including 1 subject

TABLE 20. Distribution of CHD by diagnosis group index subjects versus partners MZ and DZ pairs

	Group	MZ PARTNERS 1	2	3	4	5	*N*	DZ PARTNERS 1	2	3	4	5	*N*
	1	1	1	3	3	4	12	1	1	1	3	5	11
	2	2	—	4	1	2	9	1	—	1	1	3	6
INDEX	3	1	—	4	3	2	10	—	—	2	3	2	7
SUBJECTS	4	—	—	1	1	6	8	—	—	—	2	6	8
	5	—	1	—	1	8	10	—	1	—	2	5	8
	N	4	2	12	9	22	49	2	2	4	11	21	40

TABLE 21 Cumulative concordance rates for various CHD groups MZ and DZ pairs

	MZ				DZ				
CHD groups	Concordance Ratio	Concordance Rate, %	Age of concordant pairs Mean	S D	Concordance Ratio	Concordance Rate, %	Age of concordant pairs Mean	S D	Concordance MZ/DZ
1	1/17	5 9	(63 0)	—	1/12	8.3	(50 0)	—	0.71
1,2*	4/25	16 0	55.0	9.1	3/18	16 7	58.7	8.5	0 96
1—3	16/33	48.5	61 3	6.8	7/25	28 0	57 3	7.5	1.73
1—4	25/41	61 0	61.2	6.1	16/35	45 7	58.4	5.9	1.33

* Including 2 MZ pairs incompletely examined

dent had no cardiac symptoms but recorded negative T waves in the left lateral chest leads in the resting ECG

CONCORDANCE WITH RESPECT TO VARIOUS CHD GROUPINGS

It is evident from table 20 that both twins of one MZ and one DZ pair had infarction. If we include the 2 MZ pairs where the partners were not accurately grouped but were free of symptoms of CHD infarction was recorded in 17 MZ and 12 DZ pairs. The concordance rate for infarction will thus be 6 per cent for MZ and 8 per cent for DZ. If the criterion for CHD is extended to cover groups 1 and 2 (Table 21) the number of affected pairs—that is, pairs with at least one twin assigned to any of these 2 groups—will be 25 MZ and 18 DZ. Of these 4 MZ and 3 DZ were concordant in groups 1 and 2 The concordance rates will thus be 16 per cent and 17 per cent, respectively When the CHD criteria are widened further to take in groups 1 3 the MZ pairs whose partners did not record the exercise ECGs cannot be included because group 3 also contains cases registering ECG changes only during exercise. Sixteen of the 33 MZ pairs were concordant (48 5 per cent) against 7 of the 25 DZ pairs (28 per cent) In group 4 the CHD diagnosis was not confirmed, but if this group, too is included in the calculation of concordance the rate will be 25/41 (61 per cent) for MZ and 16/35 (46 per cent) for DZ.

The relationship between the concordance rates for the MZ and DZ pairs altered successively on including groups 1-4 (Fig. 3) The highest rate was obtained for groups 1 3 The greater number of concordant MZ than DZ pairs in groups 1 3 is not statistically significant ($0\ 05 < P < 0\ 10$)

CHD IN DISCARDED PAIRS

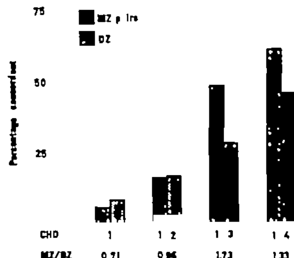
In 13 pairs selected for the study one or both twins could not be examined clinically for symptoms of CHD Five of the pairs were classed tentatively as MZ and 2 of these had been admitted to

hospital for angina pectoris or cardiosclerosis. In formation on the other 3 index subjects was not available. According to the questionnaire one of the partners of these 5 MZ pairs had neither infarction nor angina pectoris, for the other 4 no answers to the questionnaires were obtained. Of the 8 DZ index subjects 2 had been admitted to hospital for infarction and one for angina pectoris. At examination one more was found to have angina pectoris and ECG changes and was accordingly assigned to group 2, while one index subject had suspected symptoms of CHD (group 4) Three DZ index subjects could not be assessed as regards the occurrence of CHD One of the DZ partners had reported angina pectoris in the questionnaire but at the examination the symptoms were judged to be of a respiratory nature. Of the 7 remaining DZ partners 4 reported no infarction or angina pectoris and 3 did not answer the questionnaires.

Of the 91 index subjects in the completely examined pairs comprising the final material 51 were assigned to groups 1 3 and 34 to groups 4 and 5—that is, a ratio of 5 3 between these 2 categories. If the same proportion of index subjects in the incompletely examined pairs were assigned to groups 1 3 this would mean 3 of the 5 MZ and 5 of the 8 DZ index subjects. Inclusion of the 2 MZ pairs whose index partners did not perform the exercise ECG would bring to 38 the total number of MZ pairs where at least one of the twins could have been assigned to groups 1 3 The corresponding number of DZ pairs is 30 A significantly greater number of concordant MZ pairs ($P<0.05$) would be obtained only if a total of 19 of the MZ pairs and 8 of the DZ pairs were judged to be concordant. For this the concordance rate for the 5 MZ pairs thus added would need to be higher and that for the 5 added DZ pairs lower than that of the rest of the material—a possibility that cannot be ruled out, however

COMMENTS

For infarction as a manifestation of CHD there was concordance for only 2 pairs, one of them MZ. Of both these pairs one twin had died. For most of the other pairs the diagnosis of infarction was made *in vit* Infarction can, however run an asymptomatic course[182] As has been shown by Bjurulf *et al*[31] however the coronary changes tend to be less advanced in silent than symptomatic infarction. Discordance with respect to clinically confirmed infarction would therefore seem to express a significant difference in the manifestation of CHD in the co-twins. The course of CHD giving rise to infarction would appear to be influenced by modifying environmental factors, as has been pointed out by Thomas & Cohen[188] In their recent reported study of deaths from myocardial infarction among 199 male pairs Harvald & Hauge[87] found concordance in 39 per cent of the MZ and 26 per cent f the DZ pairs. This difference was not gnificant as it was for the 81 female pairs, where 44 per cent f the MZ and 15 per cent of the DZ were concordant. In 72 unlike-sexed DZ pairs the concordance was 42 per cent if the proband was femal and 13 per cent f male, from which it was concluded that in respect of the occurrence of CHD heredity would seem to be of greater significance in women than men. The environmental factors having a bearing on CHD occur to a greater extent among men and, according to these authors, diminish the significance of heredity



F gur 3 Cumulati concordance rate, successively including CHD groups 1—4 MZ/DZ quotient.

The difference in concordance for the MZ and DZ pairs was greatest if the diagnostic criteria for CHD were widened to include groups 1 3 The clinical findings for these groups were of a type such that the diagnosis of CHD was most probably correct. As above, a difference in concordance for MZ and DZ pairs in respect of a certain trait may under certain conditions be taken as an indication that the trait is governed by heredity In the case of pathologic conditions where several factors may be considered to exert an important influence or where the conditions as such are difficult to assess, caution is indicated in the interpretation of a concordance comparison. In such a situation it is impossible to accept a null hypothesis regarding the significance of heredity based on a non-significant difference in the number of MZ and DZ concordant pairs.

In the present investigation it was however found that nearly one half of the MZ pairs, against about one quarter of the DZ pairs, were concordant with respect to clinical signs of probable CHD Despite the non significant difference in concordance rates account must be taken of the dependence of genetic factors for clinical CHD in the wide sense of the term.

Intrinsic factors

PRINCIPLES OF ANALYSIS

In accordance with the object of the investigation the correlation between intrinsic factors and the presence or absence of CHD was analysed in *discordant* pairs. The results of this analysis were compared with those of a comparison of 2 groups of pairs *concordant* with respect to the probable presence (pC) and the probable absence of CHD (pnC)

The importance of heredity for the factors in question was analysed by examining the intra pair difference for each factor in the MZ and DZ pairs. For the continuous variables the intra pair variance was analysed, and for the discontinuous variables (diabetes mellitus) the concordance.

DISCORDANT PAIRS

As described in *Sect. III* the various manifestations of CHD were classified according to 4 groups of which nos. 1 3 comprised infarction, angina pectoris and/or pathologic ECG findings —signs and symptoms pointing to the probable presence of CHD In 17 MZ and 18 DZ pairs only one twin was assigned to any of the groups 1 3 The co-twins in these *pC-discordant* pairs were assigned to groups 4 and 5 which comprised only suspected CHD if any—designated probable absence of CHD

Of these 35 pairs 7 MZ and 8 DZ contained one twin with infarction. In 7 additional MZ and 3 DZ pairs one twin had infarction and the co-twins were assigned to groups 2 or 3 In 2 other MZ pairs in which one twin had infarction the co-twins could not be assigned to any of the groups 3-5 because no ECG examination during exercise had been performed. In all, there were 27 pairs in which one twin had infarction and the co-twins belonged to groups 2 5 such pairs are designated *infarction-discordant*

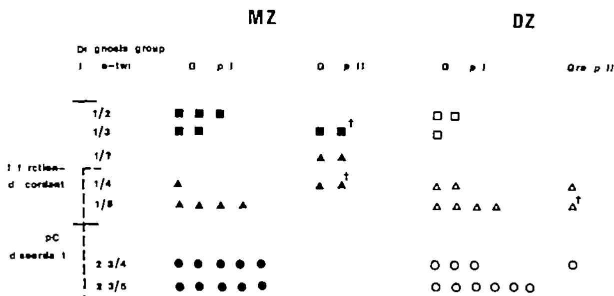
CONCORDANT PAIRS

The pairs in which the twins were concordant with respect to the probable presence (pC) and the probable absence of CHD (pnC) constitute 2 groups with the same difference in the manifestation of CHD as for the co-twins constituting the pC-discordant pairs The *pC-concordant* pairs numbered 16 MZ and 7 DZ and the *pnC-concordant* pairs 16 MZ and 15 DZ.

MATERIAL FOR THE ANALYSIS

The results concerning the intrinsic factors are based primarily on the 75 pairs—group I—both partners of which were examined at the Serafimer Hospital. In the other 16 pairs—group II—either one twin had died or the conditions of the examination did not permit the variable to be studied under comparable conditions for the co-twins The age distribution and the number of pC- and infarction-discordant pairs in group I and in the whole material divided into MZ and DZ pairs, are shown in table 22 and fig. 4

Of the 75 pairs in *group I* 10 MZ and 6 DZ pairs were concordant with respect to the probable presence of CHD (pC) The numbers of pnC-concordant MZ and DZ pairs were 29 As the mean age was lower (54.2 years) than for the pC-con



F gur 4 Pairs discordant with respect to infarction and the probable presence of CHD (pC) Intra-pair difference in diagnosis groupings groups I and IL

Group I Co-twins examined at the Serafimer Hospital
II Twins at home or through hospital records
† Pairs in which one twin died during the investigation period
No diagnosis groupi g exercise ECG not available

cordant pairs, 16 of the pnC-concordant pairs were matched with respect to age (±5 years) against the pC-concordant pairs. They were also matched with respect to zygosity (Table 22)

Of the 16 pairs constituting *group II* not submitted to an examination of intrinsic factors 10 were MZ and 6 DZ. They were on average, older than the 75 pairs of group I Nine pairs were concordant, 2 of them, both DZ, with respect to pnC and 7 to pC. The 2 infarction-discordant pairs the partners in which were not classed with respect to diagnosis groups were also included in group II. Infarction was diagnosed in a total of 10 pairs in group II, 7 of them MZ, 8 of the pairs were infarction-discordant.

The accessible information concerning the factors studied in the 16 pairs of group II will be reported in the appropriate section.

METHODS

Anthropometric variables

Height was measured to the nearest centimetre with the subject standing in bare feet.

Weight was recorded to the nearest kilogramme and included light underclothes.

Adiposity expressed as the skin-fold thickness was measured with Harpenden skin fold caliper in the triceps area of the upper right arm it is expressed as the mean of 3 measurements, to the nearest 0.2 mm.

Overweight was measured by Frisk's[22] weight/height index

$$\frac{\text{weight (kg)}}{\text{height (cm)} - 100} \times 100$$

TABLE 22 Distribution of pairs in group I[a] and I+II[b] by age: pairs discordant with respect to the probable presence of CHD and infarction; pairs concordant with respect to the probable presence (pC) and absence (paC) of CHD

		DISCORDANT PAIRS								CONCORDANT PAIRS			
		pC-discordant pairs				Infarction-discordant pairs				pC-concordant		paC-concordant	
		MZ		DZ		MZ		DZ		MZ+DZ		MZ+DZ	
	Group	I	I+II	I	I+II	I	I+II	I	I+II	I	I+II	I[a]	I+II
	N	15	17	15	18	10	16	9	11	16	23	16	31
Age	61—67	4	6	6	8	—	5	5	6	7	13	4	5
	51—60	9	9	9	10	8	9	3	4	7	7	10	17
	42—50	2	2	—	—	2	2	1	1	2	3	2	9
	Mean	56.8	57.4	58.7	59.3	55.1	57.1	59.6	59.8	58.6	60.0	57.6	54.0

[a]Co-twins examined at the Serafimer Hospital
different places (see text)
[b]Matched with respect to age and zygosity

Blood pressure

The blood pressure was measured at the beginning of the clinical examination after at least 15 minutes rest in the supine position. A mercury manometer was used on the right arm, the sleeve measured 13 by 45 cm. The systolic pressure was recorded when the Korotkoff sounds first appeared on slowly deflating the cuff from a pressure above the palpatoric, and the diastolic pressure when the sounds were fully muffled (phase 4). At least 3 measurements were performed on each subject and the lower of the 2 closest readings was recorded. The pressure was read to the nearest 5 mmHg.

Blood chemistry

Venous blood specimens for determining cholesterol, triglycerides, uric acid and creatinine in serum were drawn after an overnight fast. The analyses were performed at the Department of Clinical Chemistry, Serafimer Hospital.

Cholesterol was determined by autoanalysis by the method of Levine & Zak[124]

Triglyceride analyses were done in autoanalyzers by the method of Kessler & Lederer[118]

Uric acid was determined enzymatically by the method of Praetorius[155]

The reliability of the methods was continuously checked by determinations on standard serum.

Diabetes mellitus

The term diabetes mellitus is used here to denote the previously diagnosed disease in twins that at the time of the examination were still having antidiabetic treatment, and twins with blood sugar level above 100 mg/100 ml and glycosuria in the fasting state.

The blood glucose was determined enzymatically by Marks' method[131] in capillary specimens from the ear lobe.

Statistical methods

A comparison was made between the categories pC and paC in the discordant pairs, and between the concordant pairs assigned to these 2 categories.

The mean difference for the discordant pairs ($\bar{d}$) was compared with the difference between the means for the 2 groups of concordant pairs ($\bar{X}_{pC} - \bar{X}_{paC} = D$). The deviation from the null hypothesis ($D - \bar{d} = 0$) was examined by the t test.

In calculating the inter- and intra-pair variances for continuous variables in all the MZ and DZ pairs comprising group I the usual methods were applied[178]

The ratio between the inter- and intra-pair variances, F_1, expresses the differences between gene

tically independent twins in relation to differences between co-twins. This is true, however, only provided that the inter- and intra-pair comparisons are made under the same conditions. Age is of importance here because some of the factors examined—cholesterol, blood pressure—are in some measure dependent on age. A significantly high value of F_1 for such factors thus cannot be regarded as expressing a genetic influence only unless the material has been standardized with respect to age. The ratio between the intra-pair variance for DZ and MZ, denoted by F_2, expresses the variation in the genetically identical and less similar co-twins. A significantly high value of F_2 indicates that heredity is of importance for the variable in question.

RESULTS

Anthropometric variables

In the material as a whole the monozygotes were shorter and less heavy than the dizygotes; this is also reflected in the discordant pairs alone (Table 23). The differences in skin-fold thickness and weight/height index were, however, not significant.

For the twins who probably had CHD and those who probably had not, the differences in respect of these variables were not significant, nor were they in the discordant pairs or in the 2 groups of concordant pairs. Since, however, the mean difference of the weight/height index in the discordant MZ pairs was negative, the difference $D—\bar{d}$ was significant.

TABLE 23. Anthropometric variables in pairs discordant and concordant with respect to the probable presence (pC) and absence (poC) of CHD

		Twins I discordant pairs				Concordant pairs MZ+DZ	
		MZ		DZ			
		pC	poC	pC	poC	pC	poC
	N	15		15		16	16
Height, cm	$\bar{Y}$	170.9	170.7	172.7	175.6	171.2	172.7
	S D	*7.2*	*7.7*	*5.7*	*6.9*	*4.9*	*5.5*
Weight, kg	$\bar{Y}$	70.4	70.9	77.3	79.4	73.9	73.6
	S D	*10.4*	*10.8*	*11.6*	*11.0*	*8.9*	*8.4*
Skinfold-thickness, mm	$\bar{Y}$	8.5	8.0	10.5	10.0	9.7	9.4
		$\bar{d} = 0.54$		$\bar{d} = 0.32$		$D = 0.26$	
	S D	*2.35*		*5.08*		*2.20*	*2.03*
Significance of $D—\bar{d}$		*N.S*		*N.S*			
Weight/height index*	$\bar{Y}$	99	100	107	105	104	101
		$\bar{d} = -0.93$		$\bar{d} = 1.33$		$D = 2.56$	
	S D	*10.1*		*17.2*		*11.1*	*10.2*
Significance of $D—\bar{d}$		$P < 0.05$		*N.S*			

$$^*\frac{\text{Weight (kg)}}{\text{Height (cm)} - 100} \times 100$$

TABLE 24 Anthropometric variables, analysis of variance

	MZ	F_1	DZ
N	41		34
Height			
Intra-pair	1.97	8 47	16 65
F	43.80*		2 92**
Inter-pair	86 07		48 61
Weight			
Intra-pair	28 07	4 02**	112.77
F	6 12*		1.54
Inter-pair	171.73		174 01
Skinfold-thickness			
Intra-pair	3.27	2 40*	7 86
F_1	3.29**		1.61
Inter-pair	10 76		12.62

COMPARISON IN MZ AND DZ PAIRS

For both MZ and DZ the inter pair variance of height was significantly greater than the intra pair variance (Table 24) For weight and skinfold thickness a significantly greater inter than intra pair variance was found only for MZ twins For all 3 anthropometric variables the intra pair variances were significantly greater for DZ than MZ.

WEIGHT CHANGE

Only a few twins mentioned a notable change in weight in the history For 31 persons weight data were available from previous records (Table 25) Most of the subjects had undergone a change in weight, but in only few did it exceed 5 kg *Most of the subjects, irrespective of their CHD category* appeared to have lost weight.

COMMENTS

A retrospective study such as this is of limited value because the factors examined may alter owing to the disease. For example, overweight due to obesity may be intentionally reduced after symptoms of the disease have appeared. Objective data on previous weight, where such could be obtained, did not indicate that obesity consistently distinguished the subjects who probably had CHD from those that probably had not. However, the possibility of minor differences in weight between these 2 categories before symptoms of CHD began to appear cannot be ruled out. The greater difference in weight-height index between the pC and the poC category in concordant pairs than within the discordant MZ pairs would seem to indicate that overweight was associated with CHD only when genetic factors were not under control. In the discordant DZ pairs the twin who probably had CHD had the higher mean, but in these pairs, too the twins differed insignificantly and overweight seems to have been of minor importance for the CHD discordance Adiposity measured as the skin fold thickness, was not characteristic of the pC category in either discordant or concordant pairs, since no significant differences were observed.

The comparison between the MZ and DZ pairs shows how strongly height is dependent on heredity The weight and fat quantity expressed as skin fold thickness, would seem also to be under genetic influence, but since the *intra*-pair variances of the 2 latter factors in the DZ pairs did not differ significantly from the *inter* pair variances they seemed to be dependent in some degree on environmental influence. As regards height the results are largely in agreement with those reported by Takkunen[186] who however found that skinfold thickness was not governed by heredity

In Lundman's twin study[128] weight and skinfold thickness were found to be dependent on

TABLE 25 Weight change in pairs (MZ+DZ) where data were available

		Twins in discordant pairs		Twins in concordant pairs	
		pC	poC	pC	poC
Gain	≥ 5 kg	—	1	1	—
	< 5	2	—	—	—
No change		2	—	1	—
Loss	< 5 kg	7		5	2
	≥ 5	3	1	2	2

TABLE 26. Blood pressure (mmHg) pairs discordant with respect to the probable presence of CHD (pC) means

		MZ pC	MZ poC	DZ pC	DZ poC
INCLUDING PAIRS WITH INFARCTION					
	N	15		13	
Systolic B P	$\bar{X}$	155	149	150	145
	$\bar{d}$	6 0		4.6	
	S D	21.8		30 8	
Diastolic B P	$\bar{X}$	96	90	91	90
	$\bar{d}$	5 5		0 8	
	S.D	10 4		19 0	
Treatment[b]	N_t	5	2	1	1
EXCLUDING PAIRS WITH INFARCTION					
	N	10		9	
Systolic B P	$\bar{X}$	157	155	156	151
	$\bar{d}$	2.5		5 0	
	S D	21.5		35.3	
Diastolic B P	$\bar{X}$	97	94	96	95
	$\bar{d}$	3 0		0 6	
	S D	11.6		23.2	
Treatment[b]	N_t	4		1	1

[a] Excluding one pair with partner suffering from renal failure and one pair where the index subject had acute infarction

[b] Anti-hypertensive treatment

both genetic and environmental factors. The results from Bjurulf's autopsy study[30] indicates, too that adiposity is dependent on both heredity and environment.

Blood pressure

The blood pressure was analysed in all the pC discordant pairs and the pC and poC-concordant pairs in group I—with the exception of two discordant DZ pairs, the partner in one of which had renal failure due to chronic nephrocalcinosis the index subject in the other pair had acute infarction. The analysis was also performed after exclusion of pairs in which a twin had suffered from infarction for the blood pressure of persons with prior infarction can hardly be a representative risk factor for CHD In none of the analyses, however were pairs excluded in which some form of antihypertensive treatment had been used.

Higher means of the systolic and diastolic pressures were recorded for the probably CHD category (pC) in discordant MZ and DZ pairs (Table 26) In the comparison with the concordant pairs the discordant MZ and DZ pairs were therefore combined (Table 27 Fig. 5)

TABLE 27 Blood pressure (mm Hg) pairs discordant and concordant with respect to the probable presence (pC) and absence (poC) of CHD means

		Twins in discordant pairs MZ+DZ pC	Twins in discordant pairs MZ+DZ poC	Concordant pairs MZ+DZ pC	Concordant pairs MZ+DZ poC
INCLUDING PAIRS WITH INFARCTION					
	N	28[a]		16	16
Systolic B P	$\bar{X}$	153	147	146	140
		$\bar{d} = 5\ 4$		$D = 5.6$	
	S D	25 9		18.1	17 9
Significance of D–$\bar{d}$			NS		
Diastolic B P	$\bar{X}$	94	90	87	88
		$\bar{d} = 3\ 2$		$D = -0.62$	
	S.D	14 9		8.6	6.5
Significance of D–$\bar{d}$			$D < \bar{d}$		
Treatment[b]	N	6	5	3	2
EXCLUDING PAIRS WITH INFARCTION					
	N	19		8	16
Systolic B.P	$\bar{X}$	157	153	156	140
		$\bar{d} = 3\ 7$		$D = 15\ 6$	
	S D	28 0		18 8	17 9
Significance of D–$\bar{d}$			$P < 0\ 05$		
Diastolic B P	$\bar{X}$	97	94	91	88
		$\bar{d} = 1.84$		$D = 2\ 54$	
	S D	17.6		7 0	6.5
Significance of D–$\bar{d}$			NS		
Treatment[b]	N	5	3	2	2

[b] See footnote to table 26

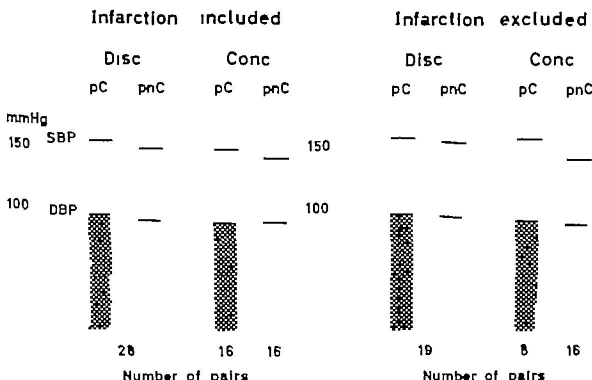


Figure 5 Blood pressure: MZ + DZ pairs discordant and concordant with respect to the probable presence (pC) and absence (pnC) of CHD. Means

The difference between the categories pC and pnC as regards the systolic pressure in the concordant pairs was significantly greater than the mean difference in the discordant pairs only when the pairs in which one twin had had infarction were excluded. There was no significant difference in diastolic pressure between categories pC and pnC except in the discordant MZ group that included pairs in which one twin had had infarction. The exclusion of the 10 pairs in which antihypertensive drugs (usually diuretics) had been used resulted in reduction of the blood pressure mean which was most obvious in the twins of discordant pairs that probably had CHD. The similarity of the pressure levels in the discordant pairs was thus not due to the inclusion of these 10 pairs.

As the blood pressure values for the majority of the twins in the 16 pairs of group II had been obtained at a home examination or from the hospital records the examination conditions were not identical and could not afford a basis for intra pair comparison. A systolic pressure in excess of 175 mmHg and/or a diastolic pressure above 110 mmHg were found in 10 persons. 4 of these belonged to discordant pairs. 3 of them probably had CHD and one probably not. One of the former had sever hypertension, and had previously had a vascular cerebral lesion and died after a myocardial infarction in connection with exacerbation of hypertension; the partner had normal blood pressure. The remaining 6 twins with an elevated blood pressure belonged to 4 pC-concordant MZ

TABLE 28 Blood pressure analysis of variance

	MZ	F_2	DZ
N	26		20
Systolic B P			
Intra-pair	241.6	< 1	158.3
F_1	2.20*		1.89
Inter pair	531.6		299 3
Diastolic B P			
Intra-pair	65 9	< 1	65 1
F	1 39		1.58
Inter pair	91 7		103.2

pairs. In the rest of the 16 pairs, whether MZ or DZ, the pressure was about the same for the co-twins, but slightly higher than for the 75 pairs belonging to group I

COMPARISON IN MZ AND DZ PAIRS

The analysis of the intra- and inter pair variances in MZ and DZ pairs comprised only the group I pairs where neither twin was receiving antihypertensive treatment and had not had infarction (Table 28) The inter pair variances were significantly greater than the intra pair variances only for the systolic pressure in the MZ pairs. On the other hand, the intra pair variances in the MZ pairs were not less than those in the DZ pairs.

COMMENTS

It is hardly practicable to draw inferences on the causal significance of the blood pressure for CHD on the basis of measurements in persons with already established disease. It will suffice here to remark that the twins that probably had CHD but not verified infarction had on average a higher systolic blood pressure than the twins that probably did not have CHD when heredity was not under control The results are in line with those obtained in the Los Angeles Heart Study[83] in which persons developing CHD manifested as angina pectoris unaccompanied by demonstrable infarction tended to have an elevated blood pressure. In the present study however those twins in the discordant pairs that probably did not have CHD recorded about the same blood pressure level as those in the probably CHD category One exception was the discordant MZ group that included pairs in which one twin had suffered from infarction this group displayed a significant intra-pair difference in diastolic blood pressure

The systolic pressure varied less within than between the MZ pairs, possibly because of the change in blood pressure with age. The results of the comparison between MZ and DZ intra pair variances afford no evidence that the blood pressure is governed by heredity The same conclusion has been reached in twin studies conducted by Downie *et al*[63] and Mathers *et al*[133] but Lundman[183] and Takkunen[184] found a closer intra pair similarity for MZ than DZ pairs It is likely that the mechanism governing blood pressure is determined to a large extent by environmental factors, some of which might show a greater similarity in sibs than in unrelated individuals.

Serum lipids

For the purpose of the analysis in group I of the cholesterol and triglyceride concentrations in serum the pairs having at least one twin with overt diabetes mellitus or thyroid disease and those undergoing nicotinic acid treatment were excluded Discordant such pairs numbered 5 MZ and 7 DZ, and concordant, 2 probably with CHD and 2 probably without.

In the *MZ pairs* the mean levels were lower for the twins that probably had CHD than for those that probably had not these differences may have been due to random variation in the small material (Table 29) The same explanation may apply to the opposite relationship for triglycerides in the *DZ pairs* As regards infarction, for both cholesterol and triglycerides non significantly lower means were obtained for twins so affected than for their discordant partners. In the comparison with the concordant pairs the discordant MZ and DZ pairs were combined (Table 30 Fig. 6) As the triglyceride values displayed a skew distribution, with the mean higher than the median, these values were converted to their logarithms. No differences in respect of the triglyceride level were

TABLE 29 Serum lipid pairs discordant with respect to the probable presence of CHD (pC) and infarction means

		MZ twins		DZ twins	
		pC	poC	pC	poC
Cholesterol	N	10		8	
(mg/100 ml)	X	283.4	299.0	294.3	294.5
	d	−15.6		−0.3	
	SD	57.9		52.5	
Triglycerides	N	9		8	
(mg/100 ml)	X	80.0	95.6	130.0	96.9
	d	−15.6		33.1	
	SD	51.2		71.1	
		MZ Infarction		DZ Infarction	
		Present	Absent	Present	Absent
Cholesterol	N	8		5	
(mg/100 ml)	X	295.3	304.5	323.6	340.8
	d	−9.3		−17.2	
	SD	50.7		66.0	
Triglycerides	N	7		5	
(mg/100 ml)	X	67.9	75.0	84.0	92.0
	d	−7.1		−8.0	
	SD	18.0		52.5	

observed between the pC and poC categories. However the difference between the mean cholesterol levels for the pC and poC-concordant pairs was significantly greater than the mean difference for the discordant pairs ($P<0.01$)

Elevated triglycerid levels (at least 150 mg/100 ml) were recorded in 14 twins 9 of these also had elevated cholesterol (at least 300 mg/100 ml) This combination, which may belong to any of the Fredrickson hyperlipo-protein patterns types III—V was found in 6 twins in the pC discordant pairs 3 of whom probably had and 3 who probably did not have CHD The remaining 3 of the 9 twins belonged to the pC-concordant pairs. Combinations of triglyceride levels of at least 100 mg/100 ml and cholesterol levels of at least 300 mg/100 ml are shown in table 31 which also

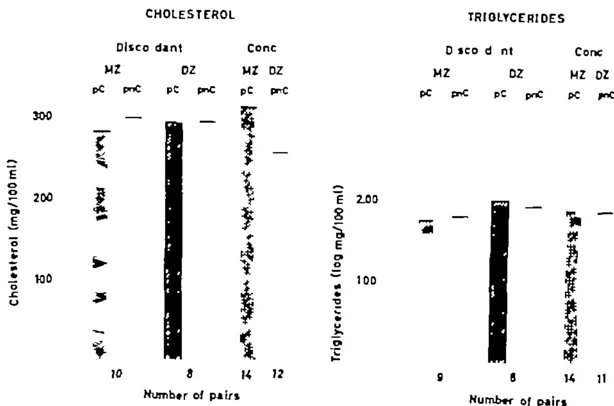
TABLE 30. Serum lipid pairs discordant and concordant with respect to the probable presence (pC) and absence (poC) of CHD means

		Twins in discordant pairs MZ+DZ		Concordant pairs MZ+DZ	
		pC	poC	pC	poC
Cholesterol	N	18		14	12
(mg/100 ml)	X	288.2	297.0	313.9	257.3
		$\bar{d} = -8.8$		$D = 56.4$	
	SD	54.3		55.1	50.8
Significance of D–d		$P < 0.01$			
Log triglycerides	N	17		14	11
(mg/100 ml)	X	1.90	1.88	1.89	1.87
		$\bar{d} = 0.02$		$D = 0.02$	
	SD	0.23		0.14	0.15
Significance of D–$\bar{d}$		NS			

TABLE 31 Elevated cholesterol and/or triglycerid levels pairs discordant and concordant with respect to the probable presence (pC) and absence (poC) of CHD. Number of subjects with endocrin disease and treated with nicotinic acid included

	Twins in discordant pairs MZ+DZ		Twins in concordant pairs MZ+DZ	
	pC	poC	pC	poC
N	30	30	32	32
Cholesterol elevated* Triglycerides	5	6	5	1
Cholesterol elevated Triglycerides not elevated	7	11	11	5
Triglycerides elevated Cholesterol not elevated	4	2	4	3
Cholesterol not elevated Triglycerides	14	11	12	23
Diabetes mellitus	4	6	1	2
Thyroid disease	—	1	—	1
Nicotinic acid treatment	3	1	1	1

*Boundary Cholesterol ≥ 300 mg/100 ml
Triglycerides ≥ 100 mg/100 ml



F gur 6 Cholesterol and log triglyceride levels (mg/100 ml) pairs discordant and concordant with respect to the probable presence (pC) and absence (pnC) of CHD Means.

takes in earlier excluded pairs with endocrine diseases and those receiving nicotinic acid treatment. It is seen that the number of twins displaying no elevation of these 2 lipid fractions did not differ for the categories pC and pnC in the discordant pairs as they did in the concordant. The number of twins recording an elevation of at least one of the lipid fractions was significantly greater in the pC-concordant than in the pnC-concordant pairs ($P<0.01$) It is also seen that an elevation of the cholesterol level, either alone or in combination with an elevation of triglycerides, tended to discriminate the 2 CHD categories better than an elevation of only the latter.

In group II, which was excluded from the above analysis, there were data relating to the cholesterol values for 10 twins from 5 MZ and 5 DZ pairs. One MZ twin in a pC-concordant pair had a cholesterol level above 300 and one DZ twin belonging to category pnC in one discordant pair recorded more than 400 mg/100 ml. This value, however was obtained in connection with thyreostatic treatment for goitre. In the remaining 8 subjects the cholesterol value was under 300 mg/100 ml.

COMPARISON IN MZ AND DZ PAIRS

The results of the analysis of the inter and intra pair variances in all the MZ and DZ pairs of group I with the exception as above of those pairs with endocrine disorders and nicotinic acid treatment are shown in table 32. In respect of the cholesterol values and the logarithm of the triglyceride values the interpair variance was significantly larger than the intra pair variance for both the MZ and the DZ pairs. The intra pair variance in cholesterol level was significantly smaller in the MZ than the DZ pairs. The triglyceride value, however, varied to the same extent within the pairs irrespective of zygosity

TABLE 32 Serum lipid analysis of [illegible]

	MZ	F_2	DZ
Cholesterol			
N	34		23
Intra-pair	875.2	1.87	1634.5
F	2.79*		3 39*
Inter-pair	2441.3		5867 1
log triglycerid			
N	32		22
Intra-pair	0 0286	< 1	0 0178
F_1	2 28*		3 41*
Inter-pair	0 0651		0 0608

COMMENTS

In the comparison between the 2 categories of concordant pairs there was a clear correlation between the cholesterol level and presence of probable CHD In this material it was not possible to distinguish between the categories pC and pnC on the basis solely of the triglyceride level. The results are in agreement with those reported by Carlson[42] for men with infarction over 50 years of age, who tended to have an elevated cholesterol level. At lower ages the rise in triglycerides was more pronounced than that of cholesterol In a Malmö series of patients hospitalized for infarction, however Björck and co-workers[22] found that those below 50 years of age had higher cholesterol values than a normal group of the same age whereas above 50 the differences were much smaller.

In the comparison between the 2 categories in the discordant pairs the differences in respect of cholesterol level were eliminated. Since the rise in cholesterol occurred to the same extent in the discordant pairs irrespective of differences in the manifestation of CHD these differences can hardly be ascribed solely to the disturbance in the lipids. The genetic influence on the cholesterol level is evident from the significantly smaller variance in the MZ than the DZ twins. There was no such evidence of heredity in respect of the triglyceride level. The greater inter than intra pair variance may be ascribed to the difference in age between the pairs In a number of the twin studies referred to earlier evidence has been adduced for a genetic influence on the cholesterol level[80, 83] while other workers have found this to be dependent also on the environment[108, 128, 131, 145, 160] The results of the present study however would appear to bear out the conclusion reached by Nevin & Slack[142] that essential hypercholesterolaemia is a genetic trait whereas lipid disorders characterized by hypertriglyceridaemia are not so strongly influenced by heredity

Uric acid

In the analyses of the serum uric acid the pairs with at least one twin treated with diuretics were excluded, as was one discordant DZ pair in which the twin that probably did not have CHD displayed signs of renal failure. Because the uric acid means in the categories pC and pnC were similar in the discordant MZ and DZ pairs, these were combined in the analyses (Table 33) The means were not significantly higher in the pC than in the pnC category either in the discordant pairs or in the 2 categories of concordant pairs

The numbers of twins for categories pC and pnC in the discordant and concordant pairs with a uric acid concentration of at least 6 mg/100 ml are shown in table 34 persons receiving diuretic therapy are included.

TABLE 33 Serum uric acid (mg/100 ml) pairs discordant and concordant with respect to the probable presence (pC) and absence (pnC) of CHD means

	Twins in discordant pairs MZ+DZ		Concordant pairs MZ+DZ	
	pC	pnC	pC	pnC
N	22		13	14
$\bar{X}$	5 00	4 83	4.75	4.78
	$\bar{d} = 0.17$		$D = -0\ 03$	
S D		*1.38*	*0.71*	*1.31*
Significance of $D - \bar{d}$			N.S.	

TABLE 34. Elevated uric acid level (≥ 6 mg/100 ml) subjects with and without diuretic treatment pairs discordant and concordant with respect to the probable presence (pC) and absence (pnC) of CHD

	Twins in discordant pairs				Twins in concordant pairs	
	MZ		DZ		MZ+DZ	
	pC	pnC	pC	pnC	pC	pnC
NO DIURETIC THERAPY						
N	11	13	14	14	29	30
≥ 6	3	4	3	2	5	4
< 6	8	9	11	12	24	26
DIURETIC THERAPY						
N	4	2	1	1	3	2
≥ 6	2	1	1	—	1	—
< 6	2	1	—	1	2	2

TABLE 35. Uric acid analysis of variance

	MZ	F_b	DZ
N_p	35		27
Intra-pair	0.59	2.26	1.34
F	3.81		< 1
Inter-pair	2.25		0.76

COMPARISON IN MZ AND DZ PAIRS

An analysis of variance disclosed a significantly greater inter- than intra-pair variation for the MZ pairs (Table 35). The intra-pair variance was significantly larger for the DZ than for the MZ pairs.

COMMENTS

No significant differences in uric acid level were observed between the twins that probably had, and those who probably did not have CHD irrespective of whether the genetic factors were under control. The analysis of inter-and intra-pair variances in MZ and DZ pairs underlines the importance of genetic factors for the uric acid and is consistent with the results obtained in previous studies[80, 108]. This material provides no support for the view that clinical manifestations of CHD are associated with an elevated uric acid level.

Diabetes mellitus

In group I pairs discordant with respect to the probable presence of CHD diabetes mellitus was found in 2 MZ and 2 DZ twins that probably had CHD. Of those probably without CHD 4 MZ and 2 DZ twins had diabetes. Of the pC-discordant MZ pairs 2 were concordant with respect to diabetes, while the pC-discordant DZ twins with diabetes belonged to different pairs. Table 36 shows how the number of diabetics was distributed with respect to treatment with insulin and/or peroral medication, and to treatment by diet or no therapy at all. The concordant pairs included one diabetic in the pC and 2 in the pnC categories.

Among the 16 pairs composing group II the presence of diabetes mellitus was established from data obtained from hospital records or from the examination. In respect of one of the co-twins in

TABLE 36. Frequency of diabetes mellitus and treatment[a] pairs discordant and concordant with respect to the probable presence (pC) and absence (pnC) of CHD group I[b] and II[c]

	Twins in discordant pairs				Twins in concordant	
	MZ		DZ		MZ+DZ	
	pC	pnC	pC	pnC	pC	pnC
GROUP I						
N	15		15		16	16
Treatment	—	3	1	2	1	1
No	2	1	1	—	—	—
Total	2	4	2	2	1	1
GROUP II						
N	1		3		6	—
Treatment	—	—	—	1	—	—
N	—	—	—	—		—
Total	—	—	—	1	2	—

[a]Treatment with insulin and/or peroral drugs.
[b]Co-twins examined at the Serafimer Hospital.
different places (see text)
[c]Pairs in which data concerning diabetes were available for both co-twins.

TABLE 37 Frequency of diabetes mellitus and treatment* in infarction-discordant pairs group I*+II*

	MZ Infarction		DZ Infarction	
	Present	Absent	Present	Absent
N	14		11	
Treatment	—	1	—	1
No	1	1	1	—
Total	1	2	1	1

*See footnote to table 36.

2 MZ and DZ pairs data were lacking. In the remaining 12 pairs there were 3 twins with previously diagnosed diabetes 2 were of a pC-concordant MZ pair one of whom had had infarction the third had probably no CHD and belonged to a discordant DZ pair

In the pairs of groups I and II that were discordant with respect to infarction 5 had diabetes mellitus (Table 37) Three of these—2 MZ and one DZ—were partners without infarction. Two with infarction had only mild diabetes, which did not call for treatment.

CONCORDANCE WITH RESPECT TO DIABETES MELLITUS

In 49 MZ and 38 DZ pairs the occurrence of diabetes mellitus could be asserted on the same basis for the twins of each pair The disease was found in 7 MZ pairs and 6 DZ pairs In 3 of the former both twins were diabetics but all 6 DZ pairs were found to be discordant in respect of this disease.

COMMENTS

Diabetes mellitus was not more prevalent among the twins of discordant pairs that probably had CHD than among the partners. Nor was the number of twins treated for diabetes greater in this category than in the pnC category The same applies to twins with infarction compared with partners in pairs discordant with respect to this condition It is notable that 11 out of the 16 diabetics were among 34 pairs discordant with respect to the probable presence of CHD but un associated with this manifestation, and that only 3 subjects with overt diabetes were found among 22 pC-concordant pairs. These results may be due to a random variation in this rather small material. The difference in CHD manifestations in the discordant pairs would however seem not to be ascribable to a higher prevalence of diabetes in the category pC or in those with infarction than in the partners. In other studies diabetics have been reported to be overrepresented among cases of CHD For instance, Sievers *et al*[173] found that the observed frequency of the disease among men with infarction aged 50—59 years was 10 times greater than expected in the general population.

The importance of genetic factors for the occurrence of diabetes could not be statistically established on the basis of the relatively few cases comprising the present twin material. The prevalence of the disease among the 98 MZ twins was 10 per cent and among the 76 DZ, 8 per cent. The expected coincidence, calculated as the square of the prevalence, will thus be 1 and 0 6 per cent, respectively There were here however 3 pairs concordant with respect to diabetes, all of them MZ The observed coincidence in the MZ group (6 per cent) thus exceeds the expected figure by a factor of 6 This is consistent with the studies of concordance in respect of diabetes in twins reviewed earlier[81, 96, 107, 187]

The occurrence of diabetes is most likely governed by genetic factors The presence of diabetes, however, was not a determining factor for the occurrence of CHD and the different manifestations of this disease in the co-twins of discordant pairs.

Combinations of intrinsic factors

The differences recorded for some of the intrinsic factors between twins that probably had and those that probably did not have CHD in the 2 categories of concordant pairs had no counterpart in the discordant pairs. The results of prospective studies[83, 103, 190] suggest that combinations of factors associated with CHD characterize more

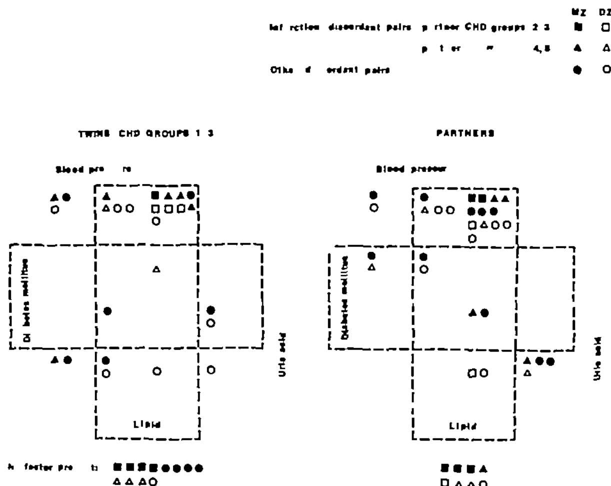


Figure 7 Combination of the 4 intrinsic factors systolic blood pressure ≥165 and/or diastolic blood pressure ≥100 mmHg, serum cholesterol ≥300 and/or triglycerides ≥150 mg/100 ml, uric acid ≥6 mg/100 ml, diabetes mellitus. Pairs discordant with respect to the probable presence of CHD and infarction.

markedly persons prone to CHD In the diagram in figure 7 twins in pC-discordant and in infarction-discordant pairs belonging to group I have been entered with respect to elevated blood pressure (SBP > 160 and DBP > 95 mmHg) elevation of lipids (cholesterol at least 300 and/or triglycerides at least 150 mg/100 ml) uric acid (at least 6 mg/100 ml) and the presence of diabetes. The diagram contains roughly as many twins that *probably had CHD as those probably without.* Furthermore, there was apparently no combination of these 4 factors that significantly discriminated between the co-twins of the infarction-discordant or pC-discordant pairs.

Comments

The analysis of intrinsic factors by comparing MZ and DZ pairs indicates that the anthropometric variables and the cholesterol and uric acid levels in serum are governed by heredity These factors would therefore not be expected to vary significantly within the discordant pairs. In the case of diabetes the small number of subjects with this disease precluded a significant statistical evaluation of the aetiologic importance of heredity for this disease, but the fact that it was found concordantly only in the MZ pairs suggests that the influence of heredity is considerable. Diabetes should consequently be included among those in-

trinsic factors that would occur to the same extent in the co-twins irrespective of the presence or absence of CHD The analysis of these intrinsic factors in the pairs concordant with respect to the probable presence and absence of CHD which constitute 2 groups without genetic resemblance, indicated that a high cholesterol and systolic blood pressure level was associated with the former category whereas for the remaining factors no significant association was found. Because diabetes was diagnosed in only a few twins of the concordant pairs, no meaningful analysis of the relationship between this disease and the probable presence of CHD could be made.

To judge from the comparison of MZ and DZ twins the blood pressure and triglyceride level are not governed by heredity It would therefore be expected that a correlation between the systolic blood pressure and the probable presence of CHD —manifested otherwise than by infarction—found in the concordant pairs would consequently also be found within the discordant pairs. The fact that this was not the case suggests that the systolic blood pressure level is more similar in sibs than in individuals from different families. That the probable presence of CHD might be associated with a high *diastolic* pressure was indicated only by the intra-pair difference found in the discordant MZ group In the present study the triglyceride level was not associated with the probable presence of CHD

As none of the intrinsic factors seem to have been responsible for the difference in the manifestation of CHD observed in the discordant pairs, these pairs were considered to constitute a suitable material for the study of extrinsic factors.

V

Extrinsic factors

The environmental factors whose association with various manifestations of CHD were examined retrospectively by means of interviews were smoking habits, physical activity and psychosocial adjustment. The dietary habits relate to actual conditions at the time of the examination and were studied chiefly as regards their association with the recorded body weight and lipid levels. The former factors were investigated with the object of ascertaining whether the environmental exposure varied with the form of manifestation of CHD so far as possible during a period that preceded any symptoms of CHD. The conditions relating to physical activity and psychosocial adjustment were thus those obtaining at about 20—40 years of age; any changes in these environmental factors after this period might be ascribed to the appearance of symptoms of CHD.

DIETARY HABITS

Material and methods

All 75 pairs examined at the Serafimer Hospital assigned to group I were questioned as regards dietary habits by means of interviews. A comparison between the probably CHD and probably not CHD categories was made *within* discordant pairs, and *between* concordant pairs (Table 22). For one of the pnC-concordant matched pairs the data on dietary conditions were incomplete.

The interviews, which lasted about 45 minutes, were performed according to Burke's seven-day recall method[40] by an experienced dietician. This requires obtaining from the subject a record of all food consumed during an average week. The mean daily caloric intake and its distribution by carbohydrate, fat and proteins were calculated from tables[2, 34]. Any change in dietary habits in the previous 3 years was recorded.

Comment

A study of individual dietary habits is a notoriously difficult task. The choice of method will depend on the type of the problem to be solved[41]. An exact registration of consumed food by measuring and weighing before and after each meal provides reliable information on the intake, but this technique incurs a risk of disturbing the usual dietary pattern. The same is true if the subject is requested in advance to record the food eaten, especially if the subject is aware that the diet analysis might be associated with any of his own symptoms of CHD; the actual choice of food might then be influenced by current discussions on the part played by diet in this disease.

Burke's method seems to afford a fairly accurate estimation of the dietary habits as regards the main constituents, including fats and carbohydrates.

Results

The twins in the discordant pairs that probably had CHD showed a lower caloric intake than their partners (Table 38), which was reflected in the fat consumption. This difference would be expected, since most of the subjects that probably had CHD restricted their physical activity because of the disease, and hence their caloric requirements were smaller. That this explanation is reasonable is evident from the differences in working capa-

TABLE 38. Daily mean consumption pairs discordant and concordant with respect to the probable presence (pC) and absence (paC) of CHD mean

		Twins in discordant pairs MZ+DZ		Concordant pairs MZ+DZ	
		pC	paC	pC	paC
	N	30		16	15
Calories, total	$\bar{X}$	2484	2795	2394	2662
		$d = -311$		$D = -268$	
	S D		850	497	584
Level of significance		$P < 0.025$		N S	
Fat, g	$\bar{X}$	106	122	103	111
		$d = -16$		$D = -8$	
	S D		45	26	28
Level of significance		$P < 0.05$		N S	
Carbohydrate, g	$\bar{X}$	276	307	271	292
		$d = -30$		$D = -21$	
	S D		110	65	61
Level of significance		N S		N S	

city* as measured during the exercise test (Table 39). As is seen from *Section IV* the differences in weight between the CHD categories were small, nor is there reason to suspect an appreciably greater loss of weight by the twins that probably had CHD than by those that probably had not. The observed dissimilarities in dietary habits were therefore probably due largely to differences in physical activity, which in turn might differ according to the CHD category.

The proportion of the total caloric intake accounted for by fat differed little for the 2 categories: for the pC twins in discordant and concordant pairs it was 37 and 39 per cent, respectively; the paC twins in the discordant pairs recorded 39 per cent against 38 for the paC-concordant pairs. Although the differences are not significant an analysis was made of whether there might be a connection between fat consumption and lipid level. The median intake of fat for all 122 twins in the discordant and concordant pairs was 106 g/day. Of 49 twins with cholesterol values of at least 300 mg/100 ml 29 had an intake in excess of the median (Table 40); the corresponding figure for 29 with a triglyceride level of at least 100 mg/100 ml was 18. The differences between these proportions and those for the twins not recording elevated lipid values are not significant, and no correlation between lipid level and fat intake in the material is indicated. Of 14

* This is denoted by W_{max} calculated as indicated by Strandell[illegible]: "the heaviest load at which the subject worked for 6 minutes with an increment proportional to the completed period at the next higher load".

TABLE 39. Working capacity (W_{max}, kpm/min) pairs discordant and concordant with respect to the probable presence (pC) and absence (paC) of CHD mean

	Twins in discordant pairs MZ+DZ		Concordant pairs MZ+DZ	
	pC	paC	pC	paC
N	30		16	16
$\bar{X}$	739	928	681	839
	$d = -189$		$D = -158$	
S D		349	197	203
Level of significance	$P < 0.001$		$P < 0.025$	

According to Strandell[illegible]

TABLE 40. Daily fat consumption and elevated serum lipid

		Mean daily intake, g ≤106	>106	N
Cholesterol	elevated*	20	29	49
	not elevated	41	32	73
	N	61	61	122
	$\chi^2 = 2.18$	$0.05 < P < 0.10$		
Triglycerides	elevated	11	18	29
	not elevated	49	42	91
	N	60	60	120
	$\chi_c^2 = 1.64$	$P = 0.10$		

* Boundary: Cholesterol ≥ 300 mg/100 ml; Triglycerides ≥ 100 mg/100 ml

TABLE 41 Daily carbohydrate consumption and elevated triglyceride

		Mean daily intake, g		
		≤271	>271	N_t
Triglycerides	≥150 mg/100 ml	3	11	14
	<150	57	49	106
	N_t	60	60	120
		$x^2 = 3.96$	$0.01 <$	$P < 0.025$

twins with an elevated triglyceride level (at least 150 mg/100 ml) (Table 41) 11 had a carbohydrate intake above the median (271 g/day) this indicates a correlation between the triglyceride level and carbohydrate consumption.

CHANGES IN DIETARY HABITS

Fifteen twins stated that they had decreased their food intake in the previous 3 years 6 of them belonged to discordant pairs, and 4 of these probably had CHD 6 others belonged to pC concordant and 3 to pnC-concordant pairs. Of these 15 all but the last 3 were distributed equally about the median fat consumption the twins in the pnC-concordant pairs all had a fat consumption below the median for these 3 exceptions the mean cholesterol level was 261 mg/100 ml. None these reporting a reduction in food intake had de a firm decision to decrease fat or to replace a imal with vegetable fat.

COMMENTS

Because the relevant conditions were obviously affected by the disease the results of the dietary examination cannot be expected to throw much light on the extent to which diet is responsible for the differences between the twins that probably had CHD and those who did not they would seem nonetheless to confirm the above findings concerning the dependence of the cholesterol level on heredity A significant lowering of this level can probably be effected only through a large enough decrease in the intake of fat and calories to produce a reduction in weight, or through a replacement of animal with vegetable fat rich in polyunsaturated fatty acids The former modification of the diet was only occasionally noted. Nor was any isocaloric diet adopted, with replacement of saturated by unsaturated fats such modifications might have lowered the cholesterol and eliminated previous differences between the categories probably CHD and probably not CHD in the discordant pairs. In other studies by Finegan et al [73] and van Buchem[28] dietary analysis also failed to show a consistent correlation between the intake of fat and the serum lipid levels in patients with CHD The observed association between carbohydrate intake and triglycerides seems to support the view held by among others, Albrink[7] and Fredrickson[78] that an elevation of this lipid fraction can be induced by a high carbohydrate intake.

SMOKING

The analysis of smoking habits, especially cigarette smoking, was approached from the standpoint of the 2 effects that have been proposed to account for the relationship between smoking and CHD namely a *chronic* one accelerating vascular atheromatosis and an *acute* effect correlated to the occurrence of infarction. The effect of smoking may thus be considered to be dependent largely on 2 factors—the duration of the smoking habit and the number of cigarettes smoked daily accordingly expressed here in terms of life-time exposure and maximum exposure, respectively

Material and methods

Information relating to smoking habits was obtained from all the pairs comprising the final material. For those examined personally a standardized questionnaire was used containing ques

TABLE 42. Smoking habits (including former) pairs discordant and concordant hb pect t the p obable presenc (pC) and absence (pnC) f CHD

	Twins in discordant pairs MZ+DZ				Twins in concordant pairs MZ+DZ			
	pC		pnC		pC		pnC	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
	35		35		46		62	
Smoking habit								
Cigarettes	21	*60*	17	*48*	25	*54*	37	*60*
Pipe cigars only	6	*17*	9	*26*	16	*35*	9	*14*
None	8	*23*	9	*26*	5	*11*	16	*26*

tions on current, daily consumption of cigarettes, cigars and pipe tobacco the duration of smoking and any changes in the habit. In the case of per sons dying before the examination could be per formed the information was obtained from the 1967 mailed questionnaire Occasionally it could be supplemented from available hospital records.

A *cigarette smoker* is defined for the purpose of this study as a person that smoked, or had previously smoked cigarettes, either exclusively or with cigars and pipe.

Other smokers current or earlier consumers of cigars and/or pipe tobacco

Non smokers persons that have not smoked any form of tobacco

Cigarette exposure is represented ( ) as the *life-time exposure* calculated as the product of the mean consumption of cigarettes a day and the duration in years (unit cigarette years) and (*u*) as the *maximum xposure* calculated as the greatest mean daily consumption of cigarettes after 40 years of age.

A comparison was made within discordant pairs and between pC-concordant and pnC-concordant pairs. The 25 pC-concordant pairs could not be matched for age with the corresponding number of pnC-concordant pairs, and the latter group was therefore eported *in tot* the mean ge was 6 years lower Thus no comparison could be made between the concordant pairs in respect of life-time exposure, and the smoking habits were accordingly analysed only in espect of the 3 smoking cate gories.

Results

SMOKING HABITS

Significantly more non-smokers were found among the pnC-concordant than pC-concordant pairs (Table 42) but in the discordant pairs the percentage of non-smokers was about the same for twins who probably had and those who probably did not have CHD As regards the number of cigarette smokers there was no significant dif ference between the 2 categories pC and pnC, nor was there between the concordant or within the discordant pairs.

Comments

In this material cigarette smoking did not discriminate twins that probably had CHD and those that probably had not In a comparison between the 2 categories of concordant pairs however account must be taken of the difference in age (Tabl 22) In the twin population at large, as in

TABLE 43 Smoking habits (including former) in male t ins born 1896—1925 one member of each pa from the S edish T in Register per cent*

		Twins born in		
		1896—1905	1906—15	1916—25
	N	941	1586	1863
Smoking habit				
Cigarettes		40 2	44.2	52.1
Pipe, cigars only		27 0	22 6	17 6
None		32.8	33 2	30 3

According to questionnaire study 1961

TABLE 44 Smoking habits life-time exposure pairs discordant with respect to the probable presence (pC) and absence (pnC) of CHD

	MZ		DZ		MZ+DZ	
	pC	pnC	pC	pnC	pC	pnC
N	17		18		35	
Life-time exposure						
Cigarettes > 450	5	6	4	5	9	11
(cig-yr) ≤ 450	7	4	5	2	12	6
Pipe, cigars only	2	3	4	6	6	9
Not exposed	3	4	5	5	8	9

the total population, the proportion of cigarette smokers—including former ones—falls with age (Table 43)

A high proportion of cigarette smokers in the pnC-concordant pairs could be ascribed to the selection procedure, involving the use of a questionnaire diagnosis of angina pectoris. This condition was shown by Cederlöf *et al*[48] to be overrepresented among smokers. No important differences in respect of smoking habits would therefore be expected in sub-samples of index subjects. As the smoking habits also proved to be similar within the pairs, the comparison between the pC and pnC-concordant pairs would give similar results. Although cigarette smokers were overrepresented in the material the number of non-smokers in categories pC and pnC differed when genetic factors were not under control.

TABLE 45 More exposed twin of pairs discordant with respect to the probable presence of CHD (pC) differing in smoking habits (MZ+DZ)

	More exposed twin	
	pC	pnC
	N = 25	
Difference in smoking habits		
Considerable[a]	6	5
Small[b]	5	9
Total	11	14

[a]More exposed twin at least 100 cig yr and at least twice as many as partner

[b]More exposed twin less difference in cig yr or pipe or cigar smoker, with partner non-smoker

LIFE TIME EXPOSURE

In the 2 CHD categories in the discordant pairs the number of non smokers was about the same. The cigarette smokers were divided into high and low life time exposure groups (Table 44) The small difference in the number of cigarette smokers was due to a greater proportion of little exposed twins who probably had CHD than of those who probably had not.

In 25 of the 35 pairs discordant with respect to category pC the co-twins differed in their smoking habits. In 11 pairs one twin had at least twice the cigarette exposure of the other (Table 45) In 14 pairs the difference was smaller. The more exposed twins were equally distributed between categories pC and pnC.

MAXIMUM EXPOSURE

The greatest mean cigarette exposure after 40 years of age was about the same for the twins with infarction as for their partners with other or no signs of CHD (Table 46)

COMMENTS

In one respect there was an association between smoking and the presence of CHD as regards the concordant pairs of the 46 twins that probably had CHD 89 per cent were smokers against 74 per cent of the 62 that probably did not have CHD. The same comparison between the 2 categories in the discordant pairs disclosed no such difference. Nor was any meaningful difference observed in these pairs in respect of cigarette exposure. As the smoking habits in several MZ and DZ pairs were fairly similar, those pC-discordant pairs where there were differences in tobacco consumption were examined. Here, too, there was no association between exposure to smoking and the probable presence of CHD. The intra-pair differences in respect of this CHD manifestation thus cannot in general be ascribed to a *chronic* effect of smo-

TABLE 46. Maximum smoking exposure ... infarction-discordant pairs

		MZ Infarction		DZ Infarction		MZ+DZ Infarction	
		Present	Absent	Present	Absent	Present	Absent
	N	16		11		27	
Maximum exposure (cig/day)	≥20	3	4	2	2	5	6
	1 19	8	6	2	2	10	8
	0	5	6	7	7	12	13

king. Nor can CHD manifested as infarction be ascribed to any *acute* effect of smoking. During the period when the majority of the infarctions occurred the proportion of heavy smokers was the same for the twins with infarction as for their partners without.

In Lundman's clinical study[128] on 196 twin pairs with different intra-pair smoking habits, there was no difference in respect of the manifestations of CHD examined. As these consisted largely of ECG changes during exercise and to a lesser extent of symptomatic CHD, the analysis of the smoking habits in pairs with symptomatic CHD supplemented the results reported by Lundman. In a questionnaire study on the whole of the Swedish twin material[49] and, moreover, in a similar study in the United States[81] correlation was found between smoking and the questionnaire symptom angina pectoris in the examination of a series of randomly selected single twins, while the comparison within MZ pairs discordant with respect to smoking habits disclosed no such association. Analyses of smoking habits in other series of infarction in males have disclosed different results from those obtained in the present study. In the prospective study of men born in 1913 and living in Göteborg[190] one half were cigarette smokers; of the 22 contracting infarction between the ages of 50 and 56 years, all but 1 were smokers. In the present study, however, more than 40 per cent of the twins in the infarction-discordant pairs were not smoking cigarettes at the time of their life when the infarctions occurred. It must be borne in mind that the Göteborg men were selected residents of a city whereas some of the twins belonged to the rural population.

PHYSICAL ACTIVITY AND PSYCHOSOCIAL ADJUSTMENT*

The other environmental factors studied are physical activity at work and during leisure time, personal conflicts, financial worries, occupational ambition and amount of overtime work. Data concerning these factors, obtained at interviews, related primarily to conditions during a period of earlier adult life when the great majority of the subjects had no symptoms.

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Material and methods

The material for this part of the investigation comprised all 85 unbroken pairs. Of the 27 pairs discordant with respect to infarction 14 MZ and 10 DZ could be examined. All 20 pairs discordant with respect to CHD groups 2–3 were examined; these will be referred to below as angina-discordant pairs, since most of the twins assigned to CHD groups 2 and 3 had angina pectoris.

at work of these only 4 twins with infarction had lower scores than their partners. All 7 twins with infarction, however that differed from their partners in respect of physical activity *during leisure time* recorded lower scores. In the angina-discordant DZ pairs all the 6 twins assigned to CHD groups 2 and 3 who differed from their partners in respect of physical activity at work had lower scores. Leisure activity did not, however discriminate the twins in the angina-discordant pairs. Physical activity involved in the journey to and from work was not correlated with any manifestation of CHD

Comments

The results provide no clear evidence that habitual physical activity as such during earlier adult life had any bearing on the presence of the various manifestations of CHD None of the twins with infarction had been engaged in more physical activity than their partners, so far as their leisure time was concerned, but one half were more active at work. Differences in respect of physical activity in leisure were observed in a study by Kasanen, Kallio & Forsström[112] in which 100 male infarction patients, most of them between 40 and 60 years, were compared with 100 controls For sports and athletics the differences were not large, but it should be noted that the control group contained more active athletes than did the infarction group

In the angina-discordant pairs a low level of physical activity at work was found to be correlated with CHD groups 2 and 3 only for the DZ twins. In the North Dakota study[218] angina pectoris occurred more often in the men engaged in strenuous physical work—farmers—than in the less physically active. However in a postmortem study by Spain and Bradess[179] there was no difference in the degree of coronary atherosclerosis in 2 groups of men without clinical CHD who differed with respect to occupational physical activity

So far as physical activity *during leisure time* is concerned, the results are in agreement with those of the Health Insurance Plan Study[171] here, for persons with sedentary living habits both at work and in leisure time the risk of infarction was considerably greater than that of other manifestations of CHD In respect of physical activity *at work* the results are at variance with those of the above investigation, and of the prospective study in Göteborg[190] The post infarction series reported by Forssman & Lindegård[74] however displayed no difference from a control group as regards occupational physical activity

In the Stockholm Prospective Study performed on a material comprising some 6500 persons, Carlson & Lindstedt[42] found that the men with no pathologic manifestations who stated that they were much engaged in physical activity outside work in general recorded lower cholesterol levels than other healthy men, but this was not the case for activity connected with work. It is therefore open to question whether there is a selective factor linking the amount of leisure physical activity with a weaker predisposition for CHD in the present material little physical activity during leisure time would seem, however to be associated with infarction irrespective of genetic factors. Since little physical activity in work did not account for the difference in the occurrence of infarction in the discordant pairs it would seem that these differences are ascribable to other factors than physical activity *per se*

PSYCHOSOCIAL ADJUSTMENT OUTSIDE WORK

It is seen from table 49 that personal conflicts did not discriminate the members of discordant pairs In 7 of the 24 discordant MZ pairs differences were recorded with respect to financial worries, and in all of them the score for this factor was higher for the twin with the more severe manifestation of CHD The proportion of more affected twins was approximately the same for those engaging in more and those engaging in less activities outside work compared with their partners.

Comments

Twins would hardly be expected to differ greatly in respect of environmental conditions closely associated with familial habits. However,

TABLE 49 Psycho-social adjustment outside work: most affected twin in infarction-discordant and angina (group 2,3) discordant pairs

		MZ twins		DZ twins		MZ+DZ twins	
		Infarction	CHD 2,3	Infarction	CHD 2,3	Infarction	CHD 2,3
	N	*14*	*10*	*10*	*10*	*24*	*20*
Psycho-social adjustment compared to partner							
Conflicts	More	4	1	2	1	6	2
	Equal	6	5	7	6	13	11
	Less	4	4	1	3	5	7
Financial worries	More	4	5	—	2	4	5
	Equal	10	7	7	7	17	14
	Less	—	—	3	1	3	1
Activities outside work	More	2	4	3	3	5	7
	Equal	8	3	2	5	10	8
	Less	4	3	5	2	9	5

in the MZ pairs where differences as regards financial worries were noted, the higher scores were recorded exclusively for the more affected twins. The results are in agreement with those reported by among others Kasanen *et al*[113]

Twins with infarction would seem not to have been more prone to personal conflict situations—including marital—than their partners. This result is inconsistent with those reported by Bruhn *et al*[37] for a population in Pennsylvania in which marital problems were more often found in a group of 80 persons with CHD than in a control group. Since, however, there were other differences between these 2 groups—anxiety cholesterol level—the question of the importance of genetic factors for the differences in CHD also arises here.

Activities during leisure time would seem not to discriminate the more affected twins from their partners. Less engagement in leisure activities by some was off-set by greater engagement by others. Rosenman & Friedman found that great activity throughout the day characterized individuals with a behaviour pattern predisposing for CHD[187] The excess energy that is reflected in this pattern might well, however also be expended through a corresponding amount of activity at work, at the expense of the opportunity for leisure pursuits. In Kasanen's study[113] fewer infarction patients than controls belonged to any clubs, but of those engaged in such leisure activities it would seem that the infarction cases often held responsible positions.

With the exception of financial worries the social factors associated with the non-vocational environment would appear not to have been of causal significance for intra pair differences in the manifestations of CHD

PSYCHOSOCIAL ADJUSTMENT AT WORK

As is seen from table 50, in only a few pairs in each discordance group did the co-twins differ in respect of *personal conflicts* in connection with work. Among the few twins with infarction recording different scores from their partners the number with more conflicts than their partners tended to be greater

Of the 13 infarction-discordant pairs in which differences in respect of occupational *ambition* were observed 10 twins with infarction gave higher scores than their partners. Just as for personal conflicts, the differences within angina-discordant pairs displayed no particular trend.

Higher scores for *overtime work* were recorded for all 6 MZ twins with infarction where an intra pair difference was observed. In the infarction-discordant DZ and the angina-discordant pairs

TABLE 50 Psycho-social adjustment in connection with work in the more affected twins in infarction-discordant and angina (group 2,3) discordant pairs

		MZ twins		DZ twins		MZ+DZ twins	
		Infarction	CHD 2,3	Infarction	CHD 2,3	Infarction	CHD 2,3
	N	*14*	*10*	*10*	*10*	*24*	*20*
Psycho-social adjustment compared to partner							
Conflicts	More	2	2	4	—	6	2
	Equal	12	7	4	8	16	15
	Less	—	1	2	2	2	3
Ambition	More	7*	1	3	2	10	3
	Equal	6	8	5	7	11	15
	Less	1	1	2	1	3	2
Overtime work	More	6	1	2	1	8	2
	Equal	8	6	4	8	12	14
	Less	—	3	4	1	4	4
Dedication to work	More	8**	2	3	3	11	5
	Equal	6	5	3	6	9	11
	Less	—	3	4	1	4	4

the more affected twins did not record higher scores more often than their partners.

Since in most cases ambition and overtime work seemed to be reflecting the same propensity namely *'dedication to work'* these 2 factors were combined by adding the scores. As is seen in the table 3 more twins with infarction and 3 with CHD group 2,3 then differed from their partners. Thus, in the infarction-discordant MZ pairs where differences were recorded for this factor all the affected twins seemed to be more dedicated to work than their partners.

Comments

Of the examined psychosocial factors associated with occupation, more ambition than their partners was found in a significant proportion of the more affected twins in the infarction-discordant pairs. In the angina-discordant pairs, however there was no similar tendency. The findings as regards infarction are in agreement with those found by Friedman & Rosenman to be characteristic of coronary prone individuals[81]. The behaviour pattern in such persons was, however considered to be due partly to genetic factors a view that finds support in the Stockholm Prospective Study[?] where men up to the age of 55 in supervisory positions recorded slightly higher lipid levels than the others. It cannot be ruled out that a selective factor might account for the association that has been found between certain psychosocial factors in conventional studies. It is interesting to note that these factors characterize persons with infarction also when genetic factors are kept under control.

PAIRS NOT EXAMINED

None of the twins of the 5 MZ pairs belonging to the discards group had infarction. In the 16 infarction-discordant MZ pairs 2 twins with infarction had died. One of them was a 66-year-old shipping clerk who together with his brother had begun training for the Navy. The one that had

Some information about psychosocial conditions regarding these 2 subjects was obtained from the questionnaires, and on one, also from the hospital records. The corresponding information relating to their partners was obtained at the examination.

since died from infarction, however at the age of 20 took a responsible position in a shipping company entailing much overtime work. The brother, assigned to the CHD group 3 continued in the Navy where he followed the usual course of advancement to the grade of petty officer in the engineering section with comparatively little exposure to occupational stress.

The other of the 2 MZ twins dying from infarction was 61 years old and had had a chequered career. From the available information it would seem that so far as ambition was concerned, he did not differ essentially from his partner. Although both were engaged on shift work, the one developing infarction had previously had a stressing job in the tailoring trade and had worked up his own business. The partner assigned to CHD group 4, would seem to have been engaged in relatively undemanding work in a subordinate position on the other hand he was occasionally faced with financial problems.

The discards included 2 DZ pairs in which one of the co-twins had had infarction. One of these, who was examined at th[illegible] fimer Hospital was 54 years old and had be[illegible] ployed as a lorry driver. By dint of hard wo[illegible] overtime he had managed to start up [illegible] business. He had occasionally been faced [illegible] ancial problems and involved in personal [illegible] As regards his twin brother, a farm[illegible] no further information could be obtained [illegible] other DZ twin that had had infarction was 6[illegible] years old and head of a department, and his work had formerly been of a stressing nature. In his youth he had been a keen swimmer. His brother' was a shop-keeper and had previously devoted much of his time to competition swimming.

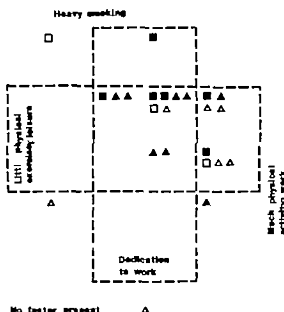
A twin in one of the 11 infarction-discordant DZ pairs included in the final material, died after an infarction at the age of 52. Like his brother he had been engaged in heavy physical work but there were no other data.

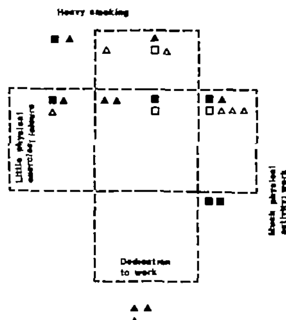
The results reported for the psychosocial factors would probably not have been affected by including the infarction-discordant pairs that had not been interviewed.

MZ DZ

First partner CHD groups 2 3 ■ □

partner " 4 5 ▲ △





No factor present

Figure 8 Combination of the 4 extrinsic factors smoking >450 cig yr dedication to work ≥4 points physical exercise at leisure <3 points physical activity in work 3 points. Infarction-discordant pairs

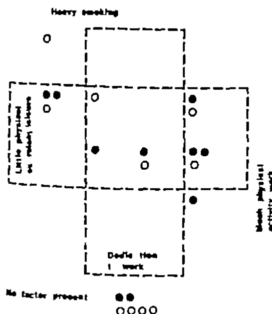
COMBINATIONS OF EXTRINSIC FACTORS

The intrinsic factors for which differences within the discordant pairs were obtained were physical activity at work and during leisure time, and dedication to work To ascertain whether there was any co-variation of these factors the twins in the discordant pairs were inserted in a diagram with respect to deviation of the respective factors from the group mean (Figs 8 and 9) To examine any possible co-variation with smoking *this factor was also included, even though it was* not correlated with any of the relevant manifestations of CHD

The co-variation was examined as regards much physical activity in work (3 points) little physical exercise during leisure time (less than 3 points) strong dedication to work (at least 4 points for ambition and overwork combined) and heavy cigarette smoking (more than 450 cigarette years)

It is evident from the diagram that so far as the twins with infarction were concerned—but not their partners—the combination of dedication to work and little physical exercise was the most typical one. Of the 4 partners in infarction-discor*dant pairs with this combination of extrinsic fac*tors, however, 2 had been assigned to CHD groups 2 or 3 and the degree of CHD discordance was therefore small. Out of the 44 more affected twins

Information obtained from hospital records



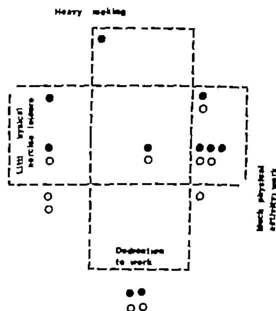


Figure 9 Combination of the 4 extrinsic factors smoking >450 cig yr dedication to work ≥4 points physical exercise at leisure <3 points physical activity in work 3 points Angina -discordant pairs.

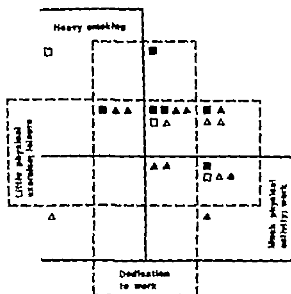
of all the discordant pairs there were 15 who had this particular combination against 6 of their partners this difference is significant

Much physical activity in work occurred more often together with little physical exercise than other combinations of all 29 twins recording the former factor 21 had had little physical exercise This combination was seen in 6 twins with infarction but in none of the un affected co-twins. The angina -discordant pairs did not display any intra-pair difference in respect of this particular combination.

C mm nt

This analysis f the combinations of 4 extrinsic factors with one exception, provides no clear evidence that the combinations are associated with the manifestations of CHD here studied. The exception is the tendency for co-variation of dedication to work and little physical exercise seen in the more affected twins of all the discordant pairs. It would seem logical that persons dedicated to work and ften working long hours should tend not to engage in physical activities in their leisure time This would seem also to be reflected in the inverse correlation between physical activity in work and during leisure time the latter ... showed that twins engaged in heavy ... often considered that this provided ... enough exercise and they accordingly de... spare to less strenuous pursuits

MZ DZ



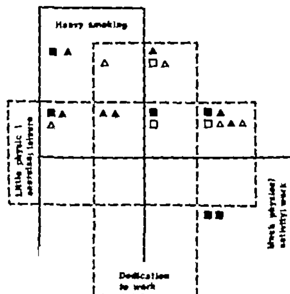


Figure 8 Combination of the 4 extrinsic factors smoking >450 cig yr dedication to work ≥4 points, physical exercise at leisure <3 points, physical activity in work 3 points. Infarction-discordant pairs

COMBINATIONS OF EXTRINSIC FACTORS

The *intrinsic factors for* which differences within the discordant pairs were obtained were physical activity at work and during leisure time, and dedication to work To ascertain whether there was any co-variation of these factors the twins in the discordant pairs were inserted in a diagram with respect to deviation of the respective factors from the group mean (Figs 8 and 9) To examine any possible co-variation with smoking this factor was also included, even though it was not correlated with any of the relevant manifestations of CHD

The co-variation was examined as regards much physical activity in work (3 points) little physical exercise during leisure time (less than 3 points) strong dedication to work (at least 4 points for ambition and overwork combined) and 'heavy cigarette smoking (more than 450 cigarette years)

It is evident from the diagram that so far as the twins with infarction were concerned—but not their partners—the combination of dedication to work and 'little physical exercise was the most typical one. Of the 4 partners in infarction-discordant pairs with this combination of extrinsic factors, however 2 had been assigned to CHD groups 2 or 3 and the degree of CHD discordance was therefore small. Out of the 44 more affected twins

Information obtained from hospital records.

CHD by comparing the concordance in MZ and DZ pairs a larger number of subjects in both zygosity groups is required, and this will become available in due course.

Discordance of coronary heart disease

The second main object of this investigation was to examine in pairs discordant with respect to CHD those factors known to be associated with this disease. The intra pair differences were in respect of groups of various CHD manifestations, the boundaries being drawn between group 1 (infarction) and the other 4 groups, to give the infarction-discordant pairs, and between groups 1 3 and 4 & 5 to give the pairs discordant in respect of the probable presence of CHD Within some of the infarction-discordant pairs, just as within the angina-discordant pairs, the differences in the manifestation of CHD were not large, but a clinically significant difference may be discerned between the 2 groups of affected and unaffected twins in the discordant pairs. The difference in diagnosed CHD may not always correspond to anatomic differences in the disease, a source of error that is probably common to all such determinations of the presence of CHD *in vivo* From practical standpoint it is the causes of symptomatic or clinically demonstrable CHD—that is, those covered by groups 1 3—that are of the greatest interest.

Factors associated with coronary heart disease

The factors examined in this investigation with respect to their possible association with certain manifestation of CHD are among those established in 1965 by a WHO working group as 'high-risk factors for CHD'[222] This Working Group on Studies on the Prevention of Ischaemic Heart Disease also found that some factors associated with CHD are predominantly under genetic influence and therefore not amenable for control. Others, gain, demand better definition and more study if one is to be in a position to estimate the value of preventive measures for such factors, which included psychogenic stress

Cross-sectional stud r cognized short comings[78 103] especially b cts through death. The value of in would be greatly limited if recor be tween factors analysed and C ply to survivors but not to cases w th However to judge from the p ospe tions, including the Framingham study are as regards most of the risk factor d ces between those dying from and those surv ing an infarction. An exception is overweight which was associated with mortality but not with the incidence of infarction. There would seem not to be any basis for supposing that a detected correlation between a certain factor and infarction would not apply to cases with a fatal outcome.

Another disadvantage of cross-sectional studies is the change that certain factors may undergo as a result of the disease—for instance, blood pressure and dietary patterns. Caution is required in deriving conclusions relating to the correlation between such factors and CHD The recording f the factors examined retrospectively—smoking and other environmental variables—may be distorted by the subjects in 2 ways ( ) Inability to recall accurately circumstances of earlier life prejudices quantitative evaluation of certain factors this would probably occur irrespective of the presence of CHD (*i*) Conscious or unconscious distortion of information owing to the presence of the disease. The tendency for the subject to attribute symptoms of the disease to some of the studied factors is, like the investigator's knowledge of clinical findings, a halo effect that should be avoided. By keeping the subject as far as possible unaware of the purpose of the study and by conceali g the clinical findings from the investigator it would seem possible to reduce this source of error considerably These precautions were taken in the present study

INTRINSIC FACTORS

An analysis of the intrinsic factors was made in discordant pairs. Any differences between the co-twins that probably had CHD and those probably without were compared with the differences between pairs concordant with respect to these 2

categories. While the former comparison that within discordant pairs, was made between genetically similar groups, the latter comparison was made between genetically unrelated groups. A correlation between a certain factor and the probable presence of CHD would presumably have been reflected as a difference in the means for the factor in the 2 categories of concordant pairs. If a factor under examination is independent of heredity or familial conditions the same difference should be obtained for the 2 categories in the discordant pairs. If however—as was the case for systolic blood pressure and cholesterol—the difference was greater for the comparison between concordant pairs than for that between the co-twins in the discordant pairs there are 2 possible interpretations either the factor in question was of a hereditary nature and therefore would not be expected to vary within the pairs or the *anatomic* differences between the categories of *clinical* CHD were in fact larger between the 2 types of concordant pairs than between the co-twins in the discordant pairs. The latter possibility cannot be ruled out, but, as mentioned earlier, the study was concerned primarily with *clinical* manifestations of CHD In this respect the categories robably CHD and probably not CHD olayed the same differences between the 2 types ncordant pairs as between the co-twins in the int pairs. The fact that for cholesterol the s between the CHD categories were sig- n t t greater between the concordant than w hin the discordant pairs would suggest that the holesterol level discriminates between these categories only when genetic factors are not under control. That this intrinsic factor is governed by heredity is seen also from the results of the intra pair comparison between the MZ and DZ pairs. For the systolic blood pressure the difference between the 2 types of concordant pairs after exclusion of twins with infarction was significantly greater than that between the twins of the 2 CHD categories in the discordant pairs. The diastolic pressure tended to be higher for MZ twins that probably had CHD than for their partners that probably had not. No such difference was observed within the discordant DZ pairs, nor between the types of concordant pairs. The intra-pair comparisons did not disclose any genetic influence on the regulation of blood pressure.

For the other intrinsic factors examined no distinct differences were observed between twins that probably had CHD and those that probably had not. Notable, however is the somewhat higher prevalence of diabetes mellitus in the discordant pairs than in either category of concordant pairs. If diabetes were typical for individuals prone to CHD it would have occurred more frequently in pairs concordant with respect to probable CHD However, because of the small size of this series the apparently contradictory result might be due to random variations. Diabetes occurred to the same extent in the twins in the discordant pairs whether or not they had CHD

Comparison of the affected and unaffected twins in discordant pairs with respect to various combinations of intrinsic factors afforded no evidence that any particular combination was typical of either the affected or the unaffected twins.

As regards the intrinsic factors it would appear that despite the observed differences in clinical CHD the discordant pairs constituted a homogenous group In this group other factors might have aggravated or elicited CHD in one of the co-twins.

EXTRINSIC FACTORS

In respect of certain extrinsic factors, unlike the intrinsic factors, twins with infarction could be distinguished from those with other manifestations of CHD The infarction-discordant pairs were therefore reported separately from the pairs discordant with respect to clinical CHD with angina pectoris as the main symptom.

Diet in this study could not be analysed as regards a causal connection with CHD because the information on dietary habits referred to the conditions at the time of the examination and they would obviously have been modified as a result of the presence of the disease.

The fact that significant differences in calory intake in the discordant pairs distinguished twins

that probably had CHD from those that probably had not suggested that these 2 categories represented by the CHD groups 1—3 and 4 & 5 differed in respect of physical performance and that the categories thus differed significantly as regards clinical manifestations of CHD

No clear relationship was observed in this material between the consumption of fat and the lipid values, whereas most twins with elevated triglycerides were found to have a carbohydrate intake above the median.

Smoking was more common in pairs where both twins probably had CHD (category pC) than pairs where no twin was assigned to this category. The number of cigarette smokers was, on the other hand, roughly the same in both these categories according to the results of the questionnaire study of the Swedish Twin Register[44] the male smokers had an excess CHD morbidity in the form of angina pectoris of 1 6 compared with non smokers, when the study covered single twins from each pair. The fact that in the present investigation the number of cigarette smokers did not differ in the 2 CHD categories of the concordant pairs having no genetic relationship may be due to the selection procedure and to the difference in age of the 2 groups for the proportion of cigarette smokers decreases with age.

Smoking habits were analysed as regards the long-term effect—*life time exposure*—in pairs discordant for the probable presence of CHD and as regards the acute effect—*maximum exposure*—in infarction-discordant pairs. No meaningful differences were observed between the groups of affected and unaffected twins. It should, however be pointed out that in many pairs the smoking habits were similar and that the material included few pairs discordant with respect to smoking, so that it does not provide suitable basis for conclusions as to the causal importance of smoking for CHD. The results are, however in line with those reported for other twin studies in Sweden and the United States[81]

Other environmental factors examined here relate to *physical activity* and *psychosocial adjustment*. The age span of about 20—40 years chosen for the examination o conditions studied usually preceded the onset symptoms of CHD by several years. To judge from the findings of, among others, Dreyfuss[61] Rab Russek[168] and Weiss[200] there is a close time rela between certain psychosocial factors and tion and this implies that because of the blank ening period some information relating to the factors possibly precipitating infarction may have been lost. Notwithstanding this, for the objective execution of the investigation this method was preferred. It is probable that more specific details relating to psychosocial adjustment nearer the onset of infarction would have proved to be correlated with this condition. A study of such relationship would, however have to be of the longitudinal type.

To permit of intra pair comparisons in the discordant pairs these environmental factors were graded according to a three-point scale. This rough grading was calculated to bring out distinct differences, and while probably resulting in some loss of information, the risk of exaggerating small intra pair differences was probably avoided. A similar method was used by Eberhard[66] in a study of environmental factors in twins with peptic ulcer

In the study of physical activity and other psychosocial factors the occupational conditions were examined separately. As intimated above, these environmental factors outside work might be considered to be associated with familial habits and thus not be expected to display significant intra pair differences. That this was the case for many of the factors studied, however, suggests that they might be governed by extra familial circumstances.

Regular physical activity, as such, did not seem to influence CHD manifested as infarction. The twins so affected generally had more strenuous occupations than their partners, whereas none had engaged in more physical activity during their leisure time. There would seem, moreover to be negative correlation between physical activity in work and during leisure time.

The study affords no clear support for the view that regular physical activity provides any protection against possible constitutional traits predispos-

Summary

Both genetic and environmental factors have been ascribed importance in the aetiology of CHD The object of the present investigation was to examine the importance of heredity for clinically demonstrable CHD and to identify environmental factors associated with the disease. The investigation was restricted to men of working age.

A suitable material for such a study is twins. Here the hereditary component of the disease can be isolated by comparing the concordance rates in monozygotic and dizygotic pairs moreover, in MZ pairs any discordance with respect to CHD must be ascribed to the environment.

The material was compiled on the basis of a questionnaire analysis of the twins comprising the Swedish Twin Register performed in 1967 it included questions relating to prior infarction and the presence of angina pectoris Of the male pairs born in the period 1900—25 1260 were tentatively classed as MZ 1860 twins answered the questionnaire and in 92 pairs one or both twins had reported symptoms of CHD

To obtain about the same number of DZ as MZ pairs the former were selected on a geographic basis from an area of Sweden that could be taken as representative of the whole country from the socioeconomic aspect. From the 904 pairs tentatively classed as DZ or of unknown zygosity 1350 twins answered the questionnaire in 78 pairs at least one twin had reported symptoms of CHD

Because it was known from previous studies that angina pectoris diagnosed on the basis of mailed questionnaires can give false positives, a preliminary interview was performed in order to establish the presence of true symptoms of CHD before the full clinical examination was performed. Likewise, in twins reporting prior infarction this diagnosis was checked against hospital records, where such were available.

Out of the 170 pairs selected by the crude questionnaire method 104 pairs remained for examination after the refined selection by means of the preliminary interview Thirteen of the 104 pairs were discarded because of loss of one of the co-twins to the examination. In 91 pairs aged 42—67 years, 51 of them MZ, a full clinical examination was performed, either at the Serafimer Hospital or in a few cases at the subject's home. The tentative zygosity classification of the Twin Register based on questionnaire statements on similarity or dissimilarity was accepted unless there was any doubt, and then a serologic determination was made.

During the period covered by the investigation, namely February 1967 to August, 1968, one of the twins in each of 6 pairs died, and information relating to the CHD diagnosis was obtained from hospital records and/or autopsy reports. For the remaining twins CHD where present, was recorded on the basis of the clinical examination, which included an ECG registration, usually during exercise.

Prior myocardial infarction was recorded on the basis of clinical or autopsy findings. A history of angina pectoris (angina of effort) was recorded in accordance with the recommendation of the London School of Hygiene and Tropical Medicine[183] To be able to compare the co-twins with respect to various manifestations of CHD these were divided into the following 4 groups

1 Myocardial infarction.
2 Angina pectoris *and* pathologic ECG findings at rest or during exercise.
3 Angina pectoris *or* ECG findings according to group 2
4. Suspected angina pectoris *or* suspected pathologic ECG findings *or* the presence of a heart

condition that precluded the possibility of a reliable CHD diagnosis.

Group 5 comprised twins without symptoms of CHD according to groups 1-4. In 8 MZ and 5 DZ pairs both twins were assigned to this group.

Eighteen MZ and 13 DZ twins had suffered from infarction (group 1) 33 MZ and 19 DZ twins were assigned to group 2 or 3

One MZ and one DZ pair were concordant with respect to infarction (group 1) One twin of each of these pairs died during the investigation period. Sixteen out of 33 MZ pairs (48 per cent) and 7 of 25 DZ pairs (28 per cent) were concordant with respect to CHD groups 1 3 where the presence of CHD was considered probable. Though this difference was not statistically significant ($0.05 < P < 0.10$) the possibility that the occurrence of clinically demonstrable CHD is governed in some degree by heredity cannot be excluded.

Sixteen MZ and 11 DZ pairs were *infarction-discordant* Seventeen MZ and 18 DZ pairs were discordant with respect to the probable presence of CHD (pC) one twin in each of these pairs was assigned to CHD groups 1 3 and their partners to group 4 or 5 which comprised twins that probably did not have CHD (pnC) Anthropometric factors, blood pressure, lipids and uric acid in serum and the presence of diabetes—here designated *intrinsic factors*—were analysed in 30 of the 35 pairs discordant with respect to the probable presence of CHD In respect of only one of these factors, namely diastolic blood pressure in the MZ pairs, was a significant difference recorded between twins assigned to the pC and those assigned to the pnC category A comparison was also made between pC-concordant and pnC-concordant pairs these 2 groups had the same difference in CHD manifestations as the co-twins f the discordant pairs but were genetically unrelated. In this comparison between the 2 groups with respect to cholesterol the differences between categories pC and pnC were significantly greater than those within the discordant pairs. The same result was obtained for the systolic blood pressure after exclusion of twin pairs where one twi had i farction. These 2 factors th.. seem to be associated with CHD only when geneti ctors are not under control.

For those infarction-discorda pairs that could also be analysed with respect to th... actors, there were no differences between the tw... with and their partners without prior infarction

An analysis of variance showed that anthropometric factors including height, weight and skin fold thickness and cholesterol and uric acid levels were in some measure governed by heredity The number of diabetics was too small for a meaningful statistical analysis of the importance of heredity for this disease, but the results point to a genetic nfluence.

The factors of an en ironmental nature analysed in interviews and designated here *extrinsic factors* included smoking, physical activity and psychosocial adjustment. These were studied with respect to conditions during a period that possibly preceded any symptoms of CHD An interview analysis was also made of the dietary habits, but this related to the pattern at the time of the examination. It was found that twins that probably had CHD had a lower caloric and fat intake than these w th probably no CHD Since there were no differences in weight between these 2 categories it was presumed that the lower caloric intake probably reflected less physical activity in the twins with more severe symptoms of CHD No significant correlation between lipid levels and fat consumption was found a high carbohydrate ntake was, however found in subjects that had elevated triglyceride values.

The twin material was found to contain a greater proportion of cigarette smokers than the male Twin Register population of the same age this was probably due to the fact that the material was selected on the basis of the questionnaire diagnosis angina pectoris Thus, there was no difference in the proportion of cigarette smokers in concordant pairs of the 2 categories pC and pnC. There was, however greater proportion of non-smokers among the pnC than in the pC-concordant pairs. N meaningful differences were found in smoking habits w thin the discordant pairs. *Lif -time ex*

posure represented by the product of the mean number of cigarettes smoked daily and the duration of smoking (in years) was the same for twins that probably had as for those that probably did not have CHD with the exception of the low exposure group which included more twins that probably had CHD. An analysis of *maximum exposure* after 40 years of age (when the majority of infarctions occurred) in the infarction-discordant pairs did not disclose differences between twins with and those without prior infarction. It was concluded that in the discordant pairs smoking could hardly have been responsible for aggravating or eliciting CHD in the more affected twins.

Extrinsic factors relating to physical activity and psychosocial adjustment were recorded according to a 3-degree scale, and intra-pair comparisons were made in 44 discordant pairs. The more affected twins in the 24 infarction-discordant and the 20 angina-discordant pairs (discordant with respect to CHD groups 2 and 3) were reported as being more, equally or less exposed than their partners. It was found that significantly more of the twins with infarction than of their partners recorded lower scores for physical exercise during leisure time than did their partners. In the angina-discordant pairs however there was a tendency for the more affected twins to have lower scores for physical activity in work than their partners.

Psychosocial adjustment outside work was not associated with any manifestation of CHD with the exception of financial worries which tended to have been more frequent in the more affected twins of all the MZ discordant pairs than in their partners.

Personal conflicts at work were not found to be a significant factor in twins with infarction or CHD group 2 or 3. Ambition and overtime work tended, however to be more frequent in the case of twins with infarction than their partners. Since in most cases these factors could be regarded as reflecting the same propensity namely dedication to work, they were combined by adding the scores. All 8 of the 14 MZ twins with infarction that differed from their partners then recorded higher scores for dedication to work. In the infarction-discordant DZ pairs and the angina-discordant pairs, however the more affected twins were not found to have been more dedicated to work than their partners.

It was concluded that genetic factors might well be of aetiologic importance for CHD in men of working age but, in addition to such factors environmental ones may aggravate or elicit the disease. Some of these factors would seem to be closely linked to the individual's attitude to his work.

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Appendix

THE "MINNESOTA CODE" FOR ECG CLASSIFICATION*

Its adaptation for the use of CR (CH) leads and for recording ECGs during and after exercise

Q and QS patterns

(Do not cod in the presence of Wolff Parkinson-White syndrome or complete LBBB)

1 1 Q/R amplitude ratio at least 1/3 *plus* Q duration of at least 0.03 s in any of leads I, II, CR_{4-7}

.2 Q duration of at least 0.04 s in any of leads I, II, $CR_{1\ 7}$

.3 Q duration of at least 0.04 s *plus* R amplitude of at least 3 mm in lead aVL

.4 Q duration of at least 0.05 s in lead III *plus* any Q wave of at least 1.0 mm amplitude in aVF

Q duration of at least 0.05 s in lead aVF

QS *pattern when* R *wave is present in the adjacent right lead on the chest in any* of leads CR_{2-7}

QS pattern in all leads $CR_{1\ 4-6}$ or $_7$

Q/R amplitude ratio of at least 1/3 *plus* Q duration of at least 0 02 s and less than 0 03 s in any of leads I, II, CR_{2-7}

duration of at least 0.03 s and less than 0.04 s in any of leads I, II, CR_{2-7}

pattern in lead II.

Q duration of at least 0.04 s and less than 0 05 s in lead III *plus* any Q wave amplitude of at least 1.0 mm in aVF

.5 Q duration of at least 0.04 s and less than 0.05 s in lead aVF

.6 Q amplitude of at least 5 mm in either of leads III, aVF

.7 QS pattern in all leads $CR_{1\ 3}$

.8 R amplitude decreasing to 2.5 mm or less and absence of RVHT and RBBB between any of leads CR_2 and CR_3, CR_3 and CR_4, CR_4 and CR_5, CR_5 and CR_6 or CR_6 and CR_7

3 1 Q/R amplitude ratio of at least 1/5 and less than 1/3 *plus* Q duration of at least 0 02 s and less than 0 03 s in any of leads I, II CR_{2-7}

.2 QS pattern in absence of LVHT in each of leads CR_1 and CR_2

.3 Q duration of at least 0.03 s and less than 0.04 s *plus* R amplitude of at least 3 mm in lead aVL

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* As modified by Åstrand *et al*[12] The figures in the original code indicating Q, S–T and T items —1, 4 and 5 respectively—have been omitted here.

4 Q duration of at least 0.03 s and less than 0.04 s in lead II e with amplitude of at least 1.0 mm in lead aVF

5 Q duration of at least 0.03 s and less than 0.04 in lead

6 QS pattern in each of leads III and aVF

S–T depressio

(Do not code in the presence of Wolff Parkins ndrome, complete LBBB RBBB or intraventricular block)

1 S–T J depression of at least 1.5 mm	CR_{2-7}
or at least 1.0 mm	I, II aVL, aVF
and S–T segment straight and slowly ascer l ng, horizontal or downward sloping	
2 S–T J depression of 1.0—1.4 mm *and* S–T segment straight and slowly ascending, horizontal or downward slop g	CR_{2-7}
3 S–T J depression of 0.5—0.9 mm *and* S–T segment straight and slowly ascending, horizontal or downward sloping	CR_{2-7} I, II, aVL aVF
4 S–T J depression less than 0.5 mm *but* S–T segment downward sloping and reaching 0.5 mm or more below P R baseline	CR_{2-7} I II, aVL aVF
5 S–T J depression less than 0.5 mm *but* S–T segment horizontal or downward sloping but reaching less than 0.5 mm below P-R baseline	CR_{2-7} I II, aVL, aVF
6 Isolated S–T J depression of at least 1.5 mm	CR_{2-7} I II, aVL aVF
or at least 1.0 mm	
S–T segment upward sloping	
7 Isolated S–T J depression of at least 0.5—1.4 mm	CR_{2-7} I, II, aVL aVF
or at least 0.5—0.9 mm	
S–T segment upward sloping	
8* Isolated S–T J depression less than 0.5 mm	CR_{2-7} I, II aVL, aVF
S–T segment upward sloping	

T wave items

(Do not code in the presence of Wolff Parkinson-White syndrome, complet LBBB RBBB or Intraventricular block)

1 T amplitude = *minus* at least 5 mm	I, II
when R amplitude = at least 5 mm	VL
when QRS mainly upright	aVF
T wave amplitude = minus at least 6.5 mm	CR_{2-7}

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* Item 8 added by the author

2 T amplitude = minus 1—5 mm (positive-negative or negative positive type)	I, II
when R amplitude = at least 5 mm	aVL
when QRS mainly upright	aVF
T wave amplitude = minus 1 5—6 4 mm	CR_{2-7}
3 T amplitude zero (flat) or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in	I, II
less than 1 5 mm in	CR_{2-7}
when R amplitude = at least 5 mm	aVL
not coded in	aVF
4 T wave low (less than 2 mm)	I, II, CR_{2-7}
if R = at least 5 mm	aVL
if QRS mainly upright	aVF